Study Aims: To determine the plasma levels of SC-58635 following oral administration of the drug in a gelatin capsule for 7 days.
Compound: SC-58635 (Lot Nº 94K014-A2B)
Dose and Route: 7.5 and 12.5 mg/kg/day (bid, po) and 20 mg/kg/day (qd, po) for 7 days
Animals: 6♂ & 6♀ beagle dogs, months of age, weighing kg.
Study Location:
Compliance with GLP: N/A
Study Design

Group	Dose (mg/kg)	Dosing Frequency	Nº of Animals
1	7.5	bid	2/sex
2	12.5	bid	2/sex
3	20	qd	2/sex

Blood Collection:

- Group 1 & 2 - 0.5, 1, 2, 3, 4, 8, 12, 12.5, 13, 14, 15, 16, 20 and 24 hr post 1st daily dose on Day1 and 0.5, 1, 2, 3, 4, 8, 12, 12.5, 13, 14, 15, 16, 20, 24, 36, 48 hr post 1st daily dose on Day 7.
- Group 3 - 0.5, 1, 2, 2.5, 3.4, 6, 8, 12, 20 and 24 hr post dose on Day 1.

Results: Individual and mean PK parameters are presented in the following table.

Dose	Time	AUC_{0-12} (μg•hr/ml)			C_{max} (μg/ml)			T_{max} (hr)		
(mg/kg)	(Day)	♂	♀	Mean	♂	♀	Mean	♂	♀	Mean
7.5	7	5.23/5.71	7.06/5.43	5.86	0.773/1.03	0.872/0.732	0.852	2.0/2.0	2.0/2.0	3.5
12.5	7	7.58/9.87	24.5/8.03	12.5	1.13/1.75	2.80/1.32	1.75	1.0/0.5	3.0/2.0	1.63
20*	1	8.93/4.68	21.9/5.3	10.2	0.763/0.304	1.69/1.03	0.947	24.0/12.0	12.0/1.5	12.4

* AUC was calculated from 0-12 hr.

3.1.4. CYNOMOLGUS MONKEY

3.1.4.1. The Pharmacokinetics And Metabolism Of SC-58635 After Intravenous Administration To The Female Cynomolgus Monkey (An Exploratory Study), Document No.: MRC-94S-0210; Date: 17-May-1995 (Vol. 1.70, p. 1-68)

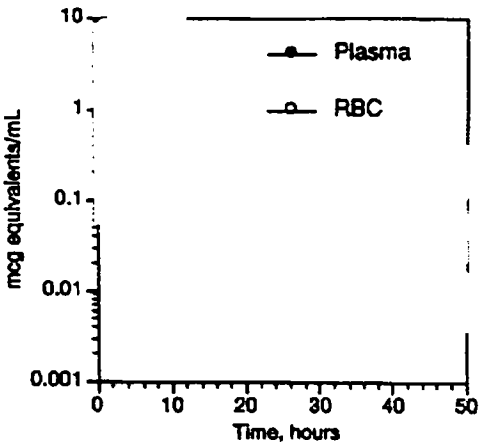
Report Nº MRC-94S-0210
Study Aim: To evaluate pharmacokinetics and metabolism of SC-58635 following intravenous bolus (1 & 15 mg/kg) ♀ cynomolgus monkey in a non-randomized crossover design
Compound: SC-58635 dissolved in PEG-400:H_2O, 2:1, v/v
Dosage & Route: 15 & 1 mg/kg, 1 ml/kg iv; each dose level was given once to each animal
Animals: 3♀ Cynomolgus monkey, weighed kg
Study Location: G.D. Searle & Co, 4901 Searle Parkway, Skokie, IL 60077
Compliance with GLP/QAU: N/A
Study Design: Each animal was given once with each dose level through the left jugular vein and the 15 mg/kg dose was given prior to 1 mg/kg dose. There was a washout period of ≥1 wk. Blood samples were collected at 0, 2, 5, 15, 30, and 45 min, and 1, 2, 3, 4, 6, 8, 12, 24, and 48 hr post dose administration. Urine and fecal samples were collected by free-catch in containers surrounded by dry ice at -18-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-160 hr. Plasma concentrations of SC-58635 were determined by the analysis.

Results: The plasmas concentrations of SC-58635 and PK parameter after iv administration at dose of 1 and 15 mg/kg to ♀ cynomolgus monkey are listed as follows:

Time (min)	Plasma Concentration (ng/ml)		Time (hr)	Plasma Concentration (ng/ml)		PK Parameters (1 mg/kg)
	[illegible]			1 mg/kg	15 mg/kg	
2						
5						
15						
30						
45						
60						

The volume of distribution was greater than total body water (≈0.7 l/kg), suggesting that SC-58635 was distributed into intracellular space and/or was bond to specific tissue sites. The major metabolite (SC-628078) of SC-58635 was eliminated through feces and urine and no parent drug was present in the excretions.

The concentrations of total in plasma and red blood cells of a female monkey following iv administration of 1 mg/kg of SC-58635 are shown in the right figure. Radioactivity partitioned into red blood cells with RBC/plasma ratio ranging from



Metabolic Profile -

Plasma: The mean percentages of total radioactivity present as SC-58635, SC-60613 and SC-62807 in are shown in following table. SC-62807 was the major circulating component in the plasma following the iv administration of a 1 mg/kg dose of SC-58635.

Time (hr)	% SC-58635	% SC-60613	% SC-62807
0.083	72.6	0	27.4
0.25	34.4	1.57	64.0
0.5	28.6	1.31	70.1
2	34.2	0.624	64.8
3	20.5	0	79.5
4	24.7	0	75.3
6	9.92	0	90.1

APPEARS THIS WAY
ON ORIGINAL

Urine and Feces: The percentage of the dose excreted in the urine as SC-58635, SC-60613 and SC-62807 were 0, 0, and 18.7%, respectively. No parent drug was excreted in the feces. The following table shows cumulative % of the dose excreted as total carbon in urine and feces, and % of dose in feces profiles present as SC-58635, SC-60613 and SC-62807 from one female cynomolgus monkey following iv administration of 1 mg/kg SC-58635.

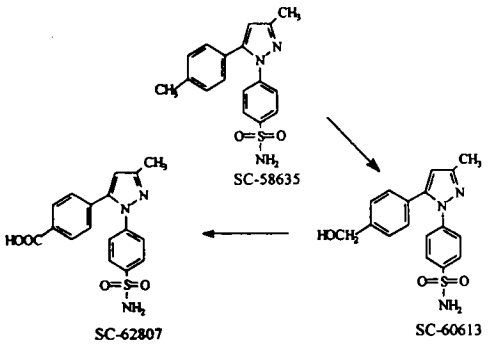
	% Dose Excreted as Total				% Dose in Feces		
Time (hr)	Urine	Feces	Urine + Feces	Time (hr)	SC- 58635	SC- 60613	SC- 62807
0 – 24	18.9	0.0215	18.9	0- 24	0	0	0.0214
0 – 48	27.0	6.38	33.4	24- 48	0	0	6.27
0 – 72	27.0	40.6	67.6	48- 72	0	0	33.8
0 – 96	27.6	53.6	81.2	72- 96	0	0	12.6
0 – 120	27.7	61.5	89.1	0- 96	0	0	52.7
0 – 144	27.8	63.3	91.1				
0 – 168	27.9	63.5	91.4				

Therefore, SC-58635 was extensively metabolized and no parent drug was excreted in urine or feces. The major metabolite of SC-58635 excreted in urine and feces was SC-62807. The major circulating metabolite of SC-58635 was SC-62807. SC-58635 was eliminated by metabolism followed by excretion of the metabolites in feces and urine.

3.1.4.2. The Pharmacokinetics And Metabolism Of SC-58635 After Intravenous Administration To The Female Rhesus Monkey (An Exploratory Study), Document No.: MRC95S-30-950167; Date: 14-Sep-1995 (Vol. 1.70, p. 69-139)

Report Nº MRC95S-30-950167
Study Aims: To determine the PK and metabolism of SC-58635 after iv administration of 1 and 15 mg/kg of SC-58635 to the female rhesus monkey in a non-randomized crossover design.
Compound: SC-58635 and SC-58635, 1 mg/ml
Vehicle: polyethylene glycol 400 (PEG): H_2O (2:1, v/v)
Dosage and Route: SC-58635 - 1 mg/kg iv; SC-58635 - 1 or 15 mg/kg iv
Animals: 3 ♀ Rhesus monkey, weighing 6.45-6.75 kg
Study Location: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077
Compliance with GLP: N/A
Study Design

Monkey ID	Compound	Dose (mg/kg)	Route	Sample Collected
581	SC-58635	15	iv	Plasma
587	SC-58635	15	iv	Plasma
588	SC-58635	15	iv	Plasma
581	[^{14}C]SC-58635	1	iv	Plasma, Urine, RBC, Feces
587	SC-58635	1	iv	Plasma
588	SC-58635	1	iv	Plasma



Sample Collection:

- Blood - 0, 2, 5, 15, 30 and 45 min, 1, 2, 3, 4, 6, 8, 12, 24, and 24 hr post dosing.
- Urine and Feces - Urine and fecal samples were collected for consecutive 24 hr periods: -18-0, 0-24, 24-48, 48-72, 72-96, 96-120, 120-144, and 144-168 hr.

Results:

- Concentrations of total radioactivity in plasma and RBC following iv injection of 1 mg/kg of SC-58635 -

Time (min)	Concentration (μg eq/ml)			Time (hr)	Concentration (μg eq/ml)		
	Plasma	RBC	RBC/Plasma Ratio		Plasma	RBC	RBC/Plasma Ratio
2				1			
5				2			
15				3			
30				4			
45				6			
				8			
				12			
				24			
				48			

- Concentration of SC-58635 in the plasma and PK parameters following iv injection of 1 and 15 mg/kg of SC-58635 -

Time (min)	Plasma Concentration (μg/ml) 1 mg/kg	15 mg/kg	Time (hr)	Plasma Concentration (μg/ml) 1 mg/kg	15 mg/kg
2			1		
5			2		
15			3		
30			4		
45			6		
PK Parameters			8		
Clp (ml/min•kg)			12		
$T_{½}$ (hr)			24	-	-
Vd (l/kg)			48	-	-
Vd_{ss} (l/kg)					

[a] value < 0.025 μg/ml (limit of detection)

APPEARS THIS WAY ON ORIGINAL

- Metabolic profiles of SC-58635 following iv injection of 1 mg/kg of SC-58635

Sample	Time (hr)	% SC-58635	% SC-60613	% SC-62807
Plasma	3			
	4			
Urine	0-24			
Feces	0.24			
	24-48			

APPEARS THIS WAY ON ORIGINAL

3.2. PROTEIN BINDING

3.2.1. RAT, MOUSE, DOG AND HUMAN

3.2.1.1. Rat And Human Plasma Protein Binding Of SC-58635 (A Pilot Study), Document No.: MRC-94S-0136; Date: 17-May-1995 (Vol. 1.70, p. 140-157)

Report Nº: MRC-94S-0136
Study Aim: To determine the extent of SC-58635 binding to protein in rat and human plasma.
Compound: SC-58635 (Lot Nº GDS-4095-25, 146 μCi/mg)
Blood Samples: Rat and Human
Study Location: G.D. Searle & Co., 800 N. Lindbergh Blvd., St. Louis, MO 63167
Compliance with QAU: N/A
Study Design: Plasma protein binding of SC-58635 was performed *in vitro* at concentrations ranging from using rat and human plasma by using a dextran-coated charcoal method.

Results: The percentages of SC-58635 bound to plasma *in vitro* are listed as follows. The binding of SC-58635 to plasma protein appeared to be concentration-dependent.

[^{14}C]SC-58635 (μg/ml)	% [^{14}C]SC-58635 bound to plasma Rat	Human
0.3	95.6	97.3
1.0	85.3	-
3.0	88.3	90.6

APPEARS THIS WAY ON ORIGINAL

3.2.1.2. The Binding Of SC-58635 To Mouse, Rat, Dog And Human Plasma Proteins, Document No.: M3097065; Date: 16-Feb-1998 (Vol. 1.70, p. 158-216)

Report Nº: M3097065
Study Aim: To determine the extent of SC-58635 binding to plasma protein in vitro for mouse, rat, dog and human, as well as for human serum albumin and human α_1

acid glycoprotein and to evaluate the plasma concentrations of free and total SC-58635 in mouse, rat and dog after oral administration of SC-58635.

Compound: SC-58635 (Lot Nº 94K031-A2A); SC-58635 (Lot Nº GDS-4671-84, in 0.5% methylcellulose (w/v) + 0.1% polysorbate 80 (v/v) suspension or in gelatin capsule.

Animals: ♂ CD-1 mice, 20-40 g; ♂ & ♀ Sprague Dawley rats, 250-350 g; ♀ Beagle dogs, 8-12 kg.

Dose: Mouse, 10 or 300 mg/kg po; Rat, 1 or 400 mg/kg po; Dog, 1 or 100 mg/kg po.

Study Location: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077.

Compliance with QAU: N/A

Study Design: The binding of SC-58635 to plasma protein was evaluated *in vivo* for mouse, rat and dog. Male Charles River CD-1 mice (n=36/dose) were administered a single dose of 10 and 300 mg SC-58635/kg in of 0.5% methylcellulose (w/v) + 0.1% polysorbate 80 (v/v) suspension. Female SD rats (n=24/dose) were administered a single oral dose of 1 or 400 mg/kg SC-58635 in of 0.5% methylcellulose (w/v) + 0.1% polysorbate 80 (v/v) suspension. Female beagle dogs (n=3) were administered single doses of SC-58635 at 1 mg/kg of suspension in 0.5% methylcellulose (w/v) + 0.1% polysorbate 80 (v/v) and 100 mg/kg capsule. Blood samples were collected from all animals after dose administration and plasma was prepared by centrifugation of blood. Plasma concentrations of total SC-58635 were determined by the method. Plasma concentrations of free SC-58635 were determined using

The binding of SC-58635 to plasma protein was evaluated *in vitro* using plasma prepared from mouse, rat, dog, and human blood and also in solutions of human serum albumin and α_1 acid glycoprotein. Blood was obtained from ♂ CD-1 mice, ♂ Sprague Dawley rats, a ♂ beagle dog, and a healthy ♂ human subject. Plasma samples for each species and the 0.067M KH_2PO_4-Na_2HPO_4 buffered (pH 7.4) solutions of human serum albumin (40 mg/ml) and human α_1 acid glycoprotein (1.80 mg/ml) were split into five equivalent aliquots that were fortified with to concentrations of 0. 1. 0.3. 1.0, 3.0 and 10 μg/ml. The protein binding of SC-58635 to plasma proteins was evaluated for each concentration using an ultracentrifugation method.

Results: SC-58635 was highly bound to plasma protein in the mouse, rat, dog and human. Data from *in vitro* plasma protein binding experiment are listed in the below table.

Species	*In Vitro* % Plasma Protein Binding SC-58635 Concentrations (μg/ml)				
	0.1	0.3	1.0	3.0	10
Mouse					
Rat					
Dog					
Human					
human α_1 acid glycoprotein					
human albumin					

Plasma C_{max} values for SC-58635 and % SC-58635 bound to protein at C_{max} following single oral administration of SC-58635 to the mouse, rat, and dog are presented in the following table.

SC-58635	Mouse	Rat	Dog
Dose (mg/kg)			
C_{max} (μg/ml)			
% Plasma Protein Binding			

3.3. TISSUE DISTRIBUTION AND ACCUMULATION

3.3.1. RAT

3.3.1.1. Tissue Distribution And Excretion Of Radioactivity Following A Single Oral Dose Of [ ]SC-58635 In Male Rats, Document No.: MRC-94S-0182; Date: 21-Jul-1995 (Vol. 1.70, p. 217-363)

Report Nº: MRC94S-0182
Study Nº 6127-226
Study Aim: To assess the tissue distribution and excretion of [ ]SC-58635 in Male Rats following a single oral dose
Compound: [ ]SC-58635 in PEG 400/H_2O
Dosage: 2 mg/kg po
Animals: 31 ♂ Long-Evans rats, weighting 196-230 g, ~51 days old.
Study Location:
Compliance with QAU: Yes
Study Design: One animal served as control and was sacrificed for the blood and tissue collection. Total 30 animals were dosed with 2 mg/kg [ ] SC-58635. The mean radioactive dose administered to each rat was 18.4 ± 0.81 μCi. Animals were sacrificed (3/time point) at 0.5, 1, 3, 8, 24, 72, 96, 144, and 168 hr postdose. Tissues and blood were collected following each sacrifice. Urine, feces and expired air were collected at selected intervals from the rats sacrificed for tissue collection at 168 hr postdose. The radioactivity in the blood, urine and feces samples and tissues distribution of radioactivity were determined.

Results: The absorption of [ ]SC-58635 was rapid; the T_{max} for the blood and plasma was 1 hr postdose with C_{max} of 4.18 and 0.966 μg equivalents/g, respectively. The highest mean C_{max} values in various tissues were liver, RBCs, blood, adrenal glands, lacrimal glands, and bone marrow, with levels of 6.28, 5.70, 4.18, 3.31, 3.24 and 2.99 μg equivalents/g, respectively. By 72 hr postdose, concentrations in the most tissues were below the limit of detection. The mean & cumulative (n=3) percent of radioactive dose in urine, and feces was presented in the following table. At 168 hr post administration, 0.71%, 14.9%, and 6.71% of radioactivity was recovered in the feces, urine and cage wash, respectively indicating that the major route of excretion was through the faces.

Collection Time (hr)	Mean % of Radioactive Dose		Collection Time (hr)	Cumulative % of Radioactive Dose	
	Urine	Feces		Urine	Feces
0-6	5.08	12.1	0-6	5.08	12.1
6-24	5.71		0-24	10.8	
24-48	1.99	50.8	0-48	12.8	46.0
48-72	0.94	13.7	0-76	13.7	59.7
72-96	0.38	9.84	0-96	14.1	69.6
96-120	0.24	0.72	0-120	14.3	70.3
120-144	0.24	0.40	0-144	14.6	70.7
144-168	0.30	0.17	0-168	14.9	70.9

3.3.1.2. The Pharmacokinetics And Metabolism Of [ ] SC-58635 After Oral Administration To the Pregnant Rat, Document No.: M3097235; Date: 22-Sep-1997 (Vol. 1.71, p. 1-81)

Study Nº: Covance 6127-328
Study Report Nº: M3097235

Study Aims: To obtain information on the PK and metabolism of SC-58635 after a single oral administration to pregnant rats and to determine whether drug-associated radioactivity reached the fetuses or the amniotic fluid.

Compound: SC-58635 (Lot Nº: GDS 4671-84,) in PEG400/H_2O (2:1), 0.5 mg/ml and 30 μCi/mg

Vehicle: PEG400/H_2O (2:1)

Dose and Route: 5 mg/10 ml/kg

Animals: 19 timed-pregnant ♀ Sprague-Dawley rats, Crl:CD®(SD)BR, weighing 303-346 g

Study Site:

Study Date: 11/20-11-21/96

GLP/AUC: N/A

Study Design: Pregnant rats were given a single oral dose of SC-58635, 5mg/kg, by gavage on Day 18 of gestation. Maternal blood, amniotic fluid and all fetuses from each animal were collected at different time as shown in the following table.

Group	Nº of Pregnant ♀	Compound	Dose (mg/ml/kg)	Sampling Time (hr)
1	1	-	-	Pre-dose
2	3	SC-58635	5/10	0.5
3	3	SC-58635	5/10	1
4	3	SC-58635	5/10	2
5	3	SC-58635	5/10	4
6	3	SC-58635	5/10	8
7	3	SC-58635	5/10	24

APPEARS THIS WAY
ON ORIGINAL

Results:

- TISSUE DISTRIBUTION OF RADIOACTIVITY - Mean (±SE) % radioactive dose and PK parameters in plasma, amniotic fluid and fetuses following a single oral dose of SC-58635 (5 mg/kg) are shown in the below table.

Sampling Time (hr)	μg Equivalent SC-58635/g		
	Plasma	Amniotic Fluid	Fetuses
0.5	0.728 ± 0.074	0.057 ± 0.018	0.444 ± 0.055
1	0.837 ± 0.143	0.052 ± 0.008	0.666 ± 0.046
2	0.814 ± 0.034	0.089 ± 0.010	0.772 ± 0.055
4	1.07 ± 0.103	0.130 ± 0.022	0.984 ± 0.104
8	2.28 ± 0.225	0.192 ± 0.012	1.51 ± 0.061
24	0.557 ± 0.04	0.066 ± 0.009	0.594 ± 0.043
PK PARAMETERS			
T_{max} (hr)	8	8	8
C_{max} (μg eq/ml)	2.28	0.192	1.51
$AUC_{0-\infty}$ (μg eq•hr/g)	37.8	3.7	30.6

APPEARS THIS WAY
ON ORIGINAL

- DISTRIBUTION OF RADIOACTIVITY IN EXTRACTS - The following table illustrates the distribution of radioactivity in extracts of samples of plasma, amniotic fluid, and fetus collected at specified times postdose for pregnant female rats following a single oral dose of SC-58635 (5 mg/kg) and analysis of extracts.

APPEARS THIS WAY
ON ORIGINAL

Hours Postdose	Composite Conc.[b]	% TR[c]	Extract Conc.	SC-62807		SC-60613		SC-58635	
				% TR	Conc.	% TR	Conc.	% TR	Conc.
PLASMA									
Control[a]									
1									
8									
24									
AMNIOTIC FLUID									
Control[a]									
1									
8									
24									
FETUS									
Control[a]									
1									
8									
24									

[a]Fortified control; [b]Concentration: μg eq/g; [c]TR = Total radioactivity

3.3.1.3. Milk Secretion Of [^{14}C] SC-58635 In The Rat, Document No.: M3097236; Date: 02-Sep-1997 (Vol. 1.71, p. 82-163)

Included as an appendix To This Report were:
Milk Secretion Of SC- 58635 In The Rat, Document No.: M2096302; Date: 29-Aug-1997 (Vol. 1.71, p. 103- 159)
Final Report Amendment No. 1: Milk Secretion Of SC-58635 In The Rat, Document No.: M3197236; Date: 24- Sep- 1997 (Vol. 1.71, p. 160- 163)

Study Nº: 6127-329
Report Nº: M3097236/M2096302
Study Aims: (1) To determine the extent of transfer of SC-58635 from maternal blood to milk in the rat and to assess the nature of the radioactive residues in plasma and milk.
(2) To determine tissue distribution of SC-58635 in rats using

Compound: SC-58635 (Lot Nº: GDS 4671-84, with 141 μCi/mg of specific activity) in PEG400/H_2O (2:1)
Dose and Route: 5 mg/kg po by gavage
Animals: 24 adult Sprague-Dawley lactating rats, Crl:CD®(SD)BR, weighing 262-358 g.
Study Site:
GLP Compliance: N/A
Study Date (In-Life): 11/13-15/1996,
Study Design: Lactating rats (4-20 days postpartum) were treated with SC-58635, 5 mg/kg, by oral gavage. Blood and milk were collected at 0.5, 1, 2, 3, 5, 8, 24 and 48 hours postdose (3/time point). Plasma and milk were assayed for total radioactivity . Plasma samples were also analyzed for SC-58635 using Samples were analyzed at

Results: The concentrations of SC-58635 in plasma and milk following a single oral administration of SC-58635 were similar. The distribution of radioactivity in extracts of plasma and milk samples collected at specified times postdose following a single oral dose of

JSC-58635 (5 mg/kg) to female lactating rats and analysis of extracts are presented in the following two tables.

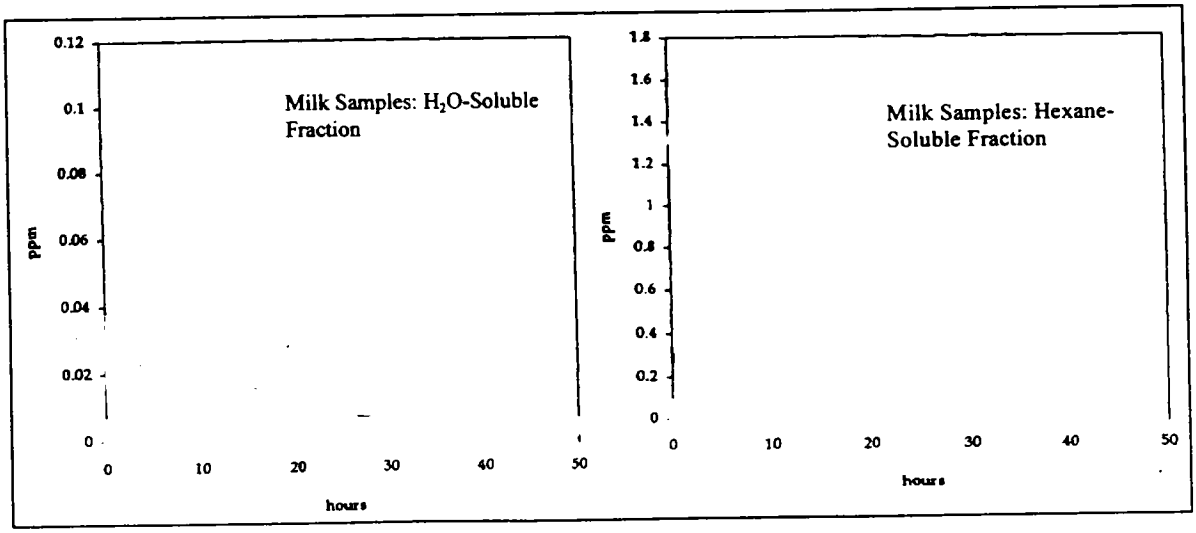
Plasma Samples		Collection Time (hr) Control	5	24
Pooled Sample Conc.				
ACN/ACN: H_2O Extract %TR				
Extracted Conc.				
SC- 62807	%TR			
	Conc.			
SC- 606 13	%TR			
	Conc.			
SC- 58635	%TR			
	Conc.			

Milk Samples		Collection Time (hr) Control	0.5	1	2	3	5	8	24	48
Pooled Sample Conc.										
Acetone: H_2O Extract										
Extracted Conc.										
%TR Aqueous 1										
%TR Aqueous 2										
		Aqueous Extract of Pooled Samples								
SC- 62807	%TR									
	Conc.									
SC- 606 13	%TR									
	Conc.									
SC- 58635	%TR									
	Conc.									

Percentages are reported to one decimal place; concentration values are reported to three decimal places.
Conc. = Concentration, μg equivalents/g; TR = Total radioactivity; NA = Not applicable; ND = Not detected.

The PK parameters for SC-58635 in plasma and milk following a single oral administration of JSC-58635 are summarized as followings.

Sample	C_{max} (μg eq/g)	T_{max} (hr)	AUC_{0-24} (μg eq•hr/ml)	$AUC_{0-\infty}$ (μg eq•hr/ml)	$T_{½}$ (hr)
Plasma					
Milk					



3.3.1.4. Tissue Distribution Of [ ] Celecoxib In Sprague-Dawley Rats Using [ ], Document No.: M2096278; Date: 24-Jun-1997 (Vol. 1.71, p. 164-210)

Study Report Nº: M2096278 96130 & M2196278
Study Aims: To determine tissue distribution of [ ]SC-58635 in rats using [ ]

Compound: [ ]SC-58635 (Lot Nº: GDS 4671-84 [ ] 14[ ]μCi/mg of specific activity) in PEG400/H_2O (2:1), 2 mg/ml for the bolus dose and 1 mg/ml for the infusion dose.
Vehicle: PEG400/H_2O (2:1)
Dose and Route: 2 mg/kg iv bolus or iv infusion at 0.4 mg/kg/hr for 5 hr
Animals: 9♂ Sprague-Dawley rats, Crl:CD®(SD)BR, ~9 weeks of age, weighing 308 g, 3/group
Study Site:
Study Date: **8/27/96-4/2/96(?) (How could the study was finished long before it was even started?)**
GLP/AUC: No
Study Design: Three groups of rats were given an iv bolus loading dose of [ ]SC-58635, 2 mg/kg, followed by an iv infusion at 0.4 mg/kg/hr for 5 hr.
Group 1 - used for
Group 2 - Tissues were processed
Group 3 - Brain was dissected, frozen and processed for metabolic profile determination. The following samples were collected for SC-58635 or radioactivity determinations.

- Blood Sampling - Blood was collected from the carotid artery (Groups 1 & 2 rats) at 1 and 4 hr after iv infusion initiated.
- Organ and Tissues - Aliquots of the liver, heart, blood, lung, brain, testes, muscle, and gut content were obtained after whole-body sectioning of frozen animals for the analysis of radioactivity.

Results: Levels of radioactivity in whole blood, plasma, and cellular fraction, and analysis of tissue radioactivity are shown in the following two tables.

Time Point	Whole Blood		Plasma		Cell Fraction		Ratios		
	Mean dpm/g	μg eq/g	Mean dpm/g	μg eq/g	Mean dpm/g	μg eq/g	Plasma/Cell Fraction	Plasma/Blood	Cell Fraction/Blood
1 hr	430518		59040		815867		0.08	0.13	2.06
4 hr	412013		68448		759310		0.09	0.18	1.90
5 hr	328975		79257		557489		0.14	0.24	1.69

Tissue	Mean dpm/g[a]	Average μg eq/g[a]	Tissue/Blood Ratio
Liver	666643	7.54	1.61
Blood	409361	4.63	1.00
Lung[b]	452950	5.13	1.15
Testes	122037	1.38	0.29
Brain	164708	1.86	0.40
Muscle	255940	2.90	0.59
Gut Content[c]	11136949	126.05	30.80
Salivary Gland	215715	2.44	0.52
Kidney'	279661	3.17	0.75

[a]Mean of 3 animals except where noted; [b] Value from one animal; [c]Mean of two animals.

APPEARS THIS WAY ON ORIGINAL

The liver, heart, lungs, kidney, and intestinal contents had the highest radioactivity. The Microradiogaphy study showed that the epithelium of the cecum and hepatocyes had specific

localization of [redacted]SC-58635. The radioactivity recovered from the brain was [redacted] and was determined to be 100% unchanged drug [redacted]SC-58635.

3.4. METABOLISM CHARACTERISTICS AND METABOLITES

3.4.1. RAT

3.4.1.1. The Isolation And Identification Of In Vivo Metabolites Of [redacted]SC-58635 In Rats, Document No.: M3094211; Date: 11-Apr-1996 (Vol. 1.71, p. 211-243)

Report Nº: M3094211

Study Aim: To determine PK and metabolism profiles and identify metabolites eliminated in bile from 3♂ rats dosed orally with 5 mg/kg of [redacted]SC-58635.

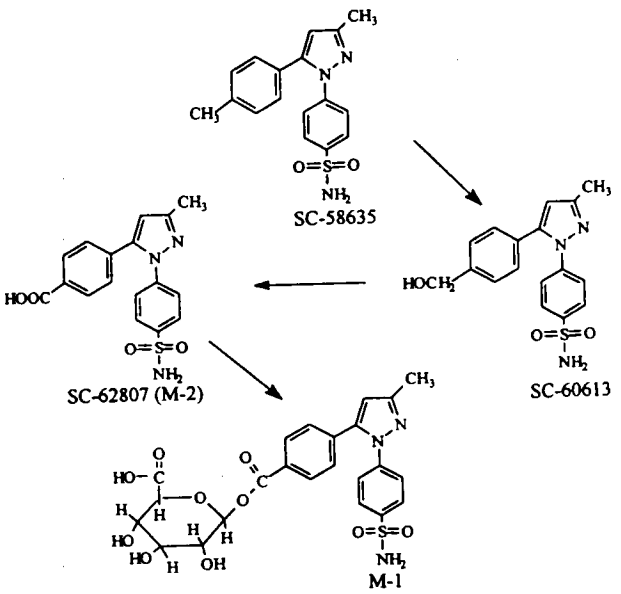
Compound: [redacted]SC-58635 in PEG 400 : H_2O (2:1, v/v)

Dose & Route: 5 mg/kg, 10 ml/kg intragastrically

Animals: 3♂ rats, weighing 297-328 g.

Study Location: G.D. Searle, Skokie, IL

Compliance with QAU: Not Indicated.



Results: Two major metabolites, SC63807 (carboxyl metabolite) and the glucuronide conjugate of SC-60613, were identified in bile. The structures of SC63807 and the glucuronide conjugate of SC-60613 are illustrated in the right figure.

3.4.1.2. Enterohepatic Circulation of [redacted]SC-58635 Following Oral Administration To The Male Rat, Document No.: M3096267; Date: 01-Dec-1997 (Vol. 1.71, p. 244-290)

Report Nº: M3096267

Study Aim: To determine the potential for enterohepatic circulation of SC-58635 in the rat

Compound: [redacted]SC-58635 (Lot Nº: GDS 4671-84, [redacted] with 141 μCi/mg of specific activity) in PEG 400 : H_2O (2:1, v/v), 2mg/ml, 5 μCi/mg; SC-58635 (Lot Nº: E90077 and 94K-031-A2A)

Dose & Route: 5 mg/kg, 10 ml/kg intragastrically

Animals: 6♂ Sprague-Dawley rats, weighing [redacted] g for donor rats and [redacted] g for recipient rats, 3/group

Study Location: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077.

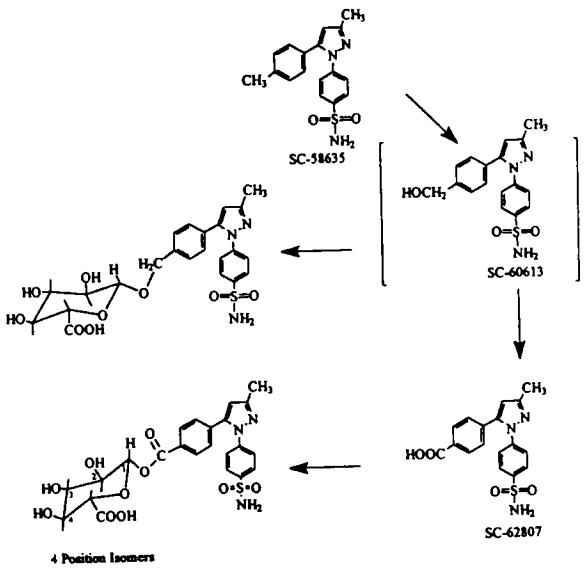
Compliance with QAU: Not Indicated.

Study Design: Six Sprague-Dawley male rats were surgically altered to allow bile to flow from a donor rat (n=3) into the duodenum of a recipient rat (n=3). [redacted]SC-58635 was administered orally at a dose of approximately 20 mg/kg to three donor rats. Blood was collected from the recipient rats (n=3) at 1, 2, 4 and 6 hr after oral dose administration to the donor rats. The donor rats were sacrificed at 6.5 hr post dose and bile was collected from the donor rats for 30 minutes immediately

prior to sacrifice. Plasma was frozen immediately on dry ice and selected samples shipped frozen to . Plasma samples were analyzed for concentrations of SC-58635 and total radioactivity. The bile was analyzed for total radioactivity and profiled by

The major metabolites in the bile extracts were identified by

Results: Concentrations of SC-58635 in the plasma collected from the three donor rats at sacrifice were 1.56, 1.93 and 0.446 μg/ml indicating that SC-58635 was systemically absorbed. There were no measurable levels (assay sensitivity limit, 0.025 μg/ml) of SC-58635 in plasma from the recipient rats, indicating that enterohepatic circulation of SC-58635 does not occur in rats administered 20 mg/kg SC-58635. Six metabolites of SC-58635 were identified in rat bile by They were SC-62807, a glucuronide conjugate of SC-60613 and four glucuronide conjugates of SC-62807. The glucuronic acid moiety of the SC-60613 glucuronide conjugate was incorporated on the hydroxyl of SC-60613. The position of the glucuronide on two of the four glucuronide conjugates of SC-62807 was determined to be on the carboxyl moiety of SC-62807. One of the SC-62807 acyl-glucuronides was a 1-O-glucuronide conjugate. The position of the glucuronide on SC-62807 was not established for the other two SC-62807 glucuronides. The sponsor stated that "It is possible that the other three glucuronide conjugates of SC-62807 are positional isomers formed as the result of acyl migration".



Proposed Metabolic Pathway of SC-58634 in Rat Bile

3.4.1.3. The Pharmacokinetics And Metabolism Of SC-58635 Following Multiple Dose Administration To The Rat, Document No.: MRC-94S-0132; Date: 07-Dec-1994 (Vol. 1.72, p. 1-256)

Report Nº	MRC-94S-0132
Study Aim:	To evaluate pharmacokinetics and metabolism of SC-58635 following oral administration for 4 weeks
Compound:	SC-58635 (Lot Nº 94L013-A1A) & SC-58635 (used on Days 1 & 26) suspension in 0.5% methylcellulose and 0.1% Tween 80
Dosage & Route:	20, 80, 400 & 600 mg/kg, 10 ml/kg, for 4 week by oral gavage
Control Vehicle:	0.5% methylcellulose and 0.1% Tween 80
Animals:	96♂ & 96♀ Sprague-Dawley rats, strain Crl:CD®(SD)BR, weighing 100 - 220 g, 3, 6 or 15/sex/ group

Study Location:
Compliance with GLP/QAU: N/A
Study Design: Group designation & dose levels were listed as followings:

Group	N° of Animals	Dose levels (mg/kg)	
1[a]	15♂ & 15♀	20	[a] Each animal received [^{14}C]SC-58635 on Days 1 & 26, and SC-58635 on Days 2 -
2[a]	15♂ & 15♀	80	25. Blood samples were taken on Days 1 & 26 at specific time (0.5, 1, 2, 3, 4, 6, 8,
3[a]	15♂ & 15♀	400	and 24 hr) post dosing from 12 animals of each group. Liver was collected from
4[a]	15♂ & 15♀	600	3/sex/group on Day 26.
5[b]	6♂ & 6♀	20	[b] Three/sex/group received a single dose of [^{14}C]SC-58635 on Day 1, and
6[b]	6♂ & 6♀	80	3/sex/group received SC-58635 on Days 1 - 25, and a dose of [^{14}C]SC-58635 on
7[b]	6♂ & 6♀	400	Day 26; urine and fecal samples were collected at specific time intervals (-24-0,
8[b]	6♂ & 6♀	600	0-24, 24-48, 48-72, 72-96, 96-120 hr) after dosing with [^{14}C]SC-58635. All
9[c]	3♂ & 3♀	20	animals were sacrificed following the last excreta collection.
10[c]	3♂ & 3♀	80	[c] Each rat received a dose of SC-58635 from Day 1 to 26 and liver was collected
11[c]	3♂ & 3♀	400	from each one following dosing on Day 26.
12[c]	3♂ & 3♀	600	

Animals were checked 2x daily for moribundity and mortality. animals were weighed on Days 1, 8, 15, 22, and 26. PK analysis was performed on blood, urine and fecal samples. Liver samples from the animals received SC-58635 were used to prepare post-mitochondrial supernatant for cytochrome P-450 analysis.

Results: The observations from the present study were summarized as following:

The PK parameters for concentrations of total in plasma following oral administration of SC-58635 on Days 1 & 26 are presented in the following table

Dose	C_{max} (µg eq/g)		T_{max} (hr)		$T_{½}$ (hr)		K (hr^{-1})		AUC_{0-t} (µg eq•hr/g)		$AUC_{0-\infty}$ (µg eq•hr/g)	
(mg/kg/day)	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Day 1												
20												
80												
400												
600												
Day 26												
20												
80												
400												
600												

The PK parameters for concentrations of total in RBC following oral administration of SC-58635 on Days 1 & 26 are shown in the following table.

Dose	C_{max} (µg eq/g)		T_{max} (hr)		$T_{½}$ (hr)		K (hr^{-1})		AUC_{0-t} (µg eq•hr/g)		$AUC_{0-\infty}$ (µg eq•hr/g)	
(mg/kg/day)	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Day 1												
20												
80												
400												
600												
Day 26												
20												
80												
400												
600												

Following oral dose administration, radioactivity was rapidly absorbed. The C_{max} of radioactivity in plasma and RBC occurred around 2 and 3 hr post dosing.

The $T_{½}$ of plasma _]SC-58635 was hr for ♂ animals and hr for ♀ rats. The hepatic cytochrome P-450 content did not change with dose, but liver radioactivity increased proportionally with dose.

The main route of excretion was through feces and the radioactive dose was extensively abolished; approximately of radioactivity was eliminated over a period of 120 hr in both ♂ and ♀ rats at all dose levels. Elimination via urinary tract was . Total radioactivity recovered was The rate, route and patter of excretion following multiple dose administration was similar to the single dose administration.

3.4.1.4. Evaluation Of The Total Radioactivity Data In a 13-Week Repeated Dose Oral Gavage Toxicity Study In Rats With SC-58635 (SA4346), Results Of Radioanalysis, Document No.: MRC95C-30-950232; Date: 09-Nov-1995 (Vol. 1.72, p. 257-369)

Report Nº: MRC95C-30-950232
Study Nº: SA4346 700-332 and 6157-183
Study Aim: To identify toxic effects of SC-58635 when administered orally by gavage to rats for at least 13 weeks.
Compound: SC-58635 (Lot Nº 94K014-A4A), SC-58635 (Lot Nº GDS 4404-145, 7.68 μCi/mg)
Vehicle: 0.5% methylcellulose (w/v) + 0.1% Polysorbate 80 (Tween® 80) (w/v) in dist. H_2O
Dosage: 0, 20, 80, 400 mg/kg/day, 10 ml/kg po for ≥ 13 weeks
Animals: 388 (194/sex) Sprague-Dawley Crl:CD®BR rats, ~6 wk old.
Study Location:
Study Date: March 16, 1995 - July 14, 1995
Radioanalysis: 22 March 1995 - 26 July 1995
Compliance with GLP/QAU: Yes

Main and Recovery[a] Study				Satellite PK Study			
Group	Dose (mg/kg/day)	Nº of Animals		Group	Dose (mg/kg/day)	Nº of Animals	
		♂	♀			♂	♀
1	0 (MC)	25	25				
2	20 (Low)	25	25	5	20 (Low)	18	18
3	80 (Mid)	25	25	6	80 (Mid)	18	18
4	400 (High)	25	25	7	400 (High)	18	18

[a] The recovery group comprised of 10/sex/group.

Experimental Design: Rats were given SC-58635, 0, 20, 80 or 400 mg/kg/day via oral gavage once daily for at least 13 weeks; dosing continued through the day prior to terminal sacrifice (Days 93/94). Recovery animals were kept without treatment for an additional 4 weeks. Rats in the satellite PK study group received SC-58635 on Days 1, 37, 86 and received nonradiolabeled SC-58635 on other days during the study. Blood were collected at 0.5, 1, 2, 4, 6, 8, and 24 hr following dosing with radiolabeled SC-58635. Urine and feces were collected at 0-24, 24-48, 48-72, 72-96, 96-120, 120-144, and 144-168 hr after radiolabeled dose administration. Plasma, red blood cells, urine, and feces were analyzed for content of radioactivity by liquid scintillation counting.

Results:

- Radioactivity in Plasma and RBC - The following table shows C_{max} and T_{max} values for radioactivity in plasma and RBC following oral administration of SC-58635 on Days 1, 37 and 86. Concentrations of radioactivity in the cellular fraction of blood were much higher than in plasma. The C_{max} values were higher in ♀ than ♂.

Sample	PK Parameters	Sampling Day	20 mg/kg		80 mg/kg		400 mg/kg	
			♂	♀	♂	♀	♂	♀
Plasma	C_{max} (μg eq/g)	1						
		37						
		86						
	T_{max} (hr)	1						
		37						
		86						
RBC	C_{max} (μg eq/g)	1						
		37						
		86						
	T_{max} (hr)	1						
		37						
		86						

- Excretion of Radioactivity- The major route of excretion of radioactivity was through the feces. Following administration of 20, 80, and 400 mg/kg of [ ] SC-58635 on Day 1 and Weeks 6 and 13, the percentage of the dosed radioactivity excreted in the feces ranged from over the 168-hour collection period with urinary excretion accounting for As the dose increased, the percentage of dosed radioactivity excreted in the feces generally increased. No changes were observed in the excretion pattern following Day 1, Week 6 and Week 13 of the dosing regimen. The following table reveals mean cumulative % radioactive dose in urine, feces, cage rinse and total radioactivity excreted during 0-168 hr period postdose with [ ] SC-58635 on Day 1, Weeks 6 and 13.

		% of Radioactive Dose							
	Dose	Urine		Feces		Cage Rinse		Total	
	mg/kg	♂	♀	♂	♀	♂	♀	♂	♀
Day 1	20								
	80	3.34 ± 0.42	3.66 ± 1.15	81.5 ± 22.5	80.9 ± 8.48	12.2 ± 17.2	10.6 ± 8.2	98.0 ± 4.77	95.4 ± 1.66
	400								
Week 6	20								
	80	4.90 ± 3.67	3.42 ± 0.91	84.8 ± 2.53	83.3 ± 7.87	4.80 ± 4.32	5.35 ± 2.95	95.1 ± 0.31	93.5 ± 5.45
	400								
Week 13	20								
	80	2.69 ± 1.34	3.28 ± 0.65	88.5 ± 3.90	85.7 ± 6.20	1.89 ± 2.26	3.34 ± 2.23	93.7 ± 3.61	94.2 ± 1.04
	400								

3.4.1.5. 26-Week Repeated Dose Oral Gavage Toxicity Study In Rats With SC-58635, SA4366, Document No.: MRC95C-30-950233; Date: 23-Feb-1996 (Vol. 1.73, p.1-71)

Report Nº: MRC95C-30-950233
Study Nº: SA4366 700-331 6157-192
Study Aim: To evaluate the chronic toxicity of SC-58635 in rats following a daily oral gavage administration for ≥26 weeks.
Compound: SC-58635 (Lot Nº 94K014-A2B), [ ] SC-58635 (Lot Nº GDS4021-68, specific activity 7.68 μCi/mg & Lot Nº 4404-145, specific activity 143 μCi/mg)
Control Vehicle: 0.5% (w/v) methylcellulose and 0.1% Polysorbate 80 in distilled H_2O
Dose & Route: 0, 20, 80, 400 mg/kg/day po by gavage
Animals: Sprague-Dawley rats, Crl:CD®(SD)BR, ~6 weeks of age, weighing g for ♂ and g for ♀, 25/sex/group for main (15/sex/group) and recovery (10/sex/group) studies, 18/sex/group for satellite PK study.
Study Location:
Compliance with GLP/QAU: Yes

Study Date (In-Life): 03/06/95 - 10/12/95

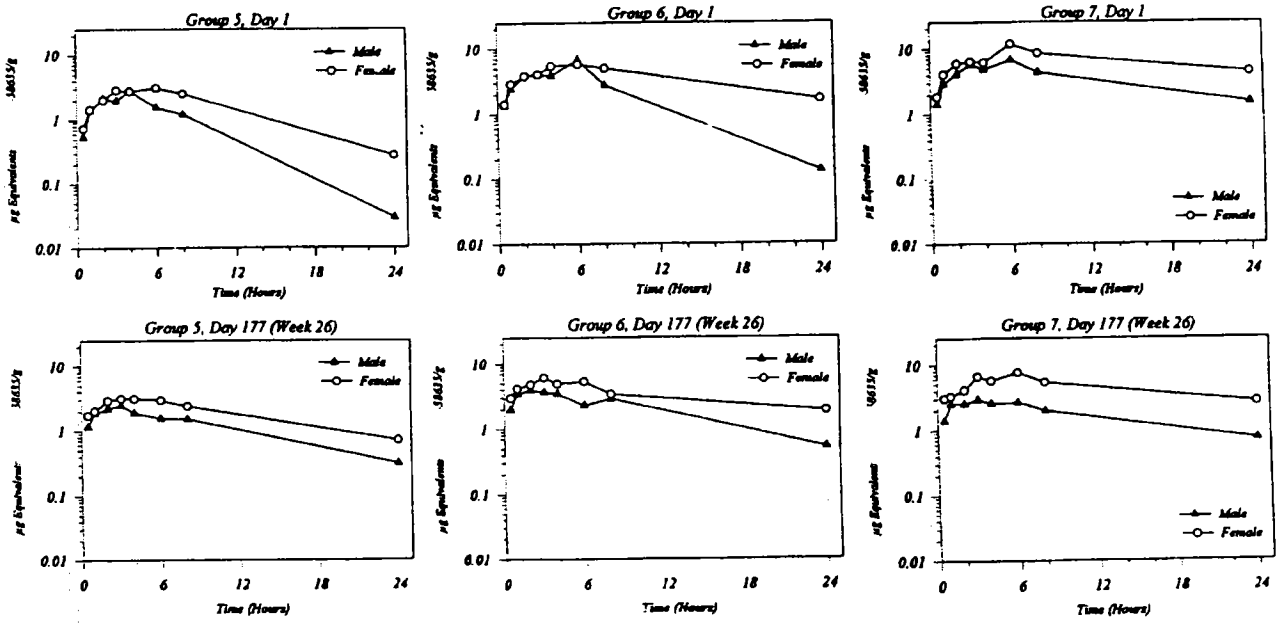
Study Design: Animals were given SC-58635, 0, 25, 80, or 400 mg/kg/day by oral gavage once daily for at least 26 weeks. Ten rats/sex from groups 1-4 were allowed to have a 4-week recovery period after the last dosing. Animal group designation and dosing levels are shown in the following table. On Days 1 and 177, SC-58635 was given to Groups 5, 6, and 7 animals. Blood samples were collected at 0.5, 1.0, 2.0, 3.0, 4.0, 8.0, and 24 hr post doing from 3 rats/sex/time point. Urine and fecal samples were collected over 168 hr after dosing with SC-58635 (Days 1 and 177) in 24 hr intervals. Plasma, red blood cells, urine, and feces were analyzed for content of radioactivity by liquid scintillation counting at the

Main and Recovery[a] Study				Satellite PK Study			
Group	Dose (mg/kg/day)	Nº of Animals		Group	Dose (mg/kg/day)	Nº of Animals	
		♂	♀			♂	♀
1	0 (MC)	25	25	5	20 (Low)	18	18
2	20 (Low)	25	25	6	80 (Mid)	18	18
3	80 (Mid)	25	25	7	400 (High)	18	18
4	400 (High)	25	25	[a]The recovery group comprised of 10/sex/group			

APPEARS THIS WAY ON ORIGINAL

Results:

- Radioactivity in Plasma and RBC- Mean concentrations of radioactivity in plasma on Days 1 and 177 for rats receiving 20, 80, and 400 mg/kg/day are shown in the following graphs.

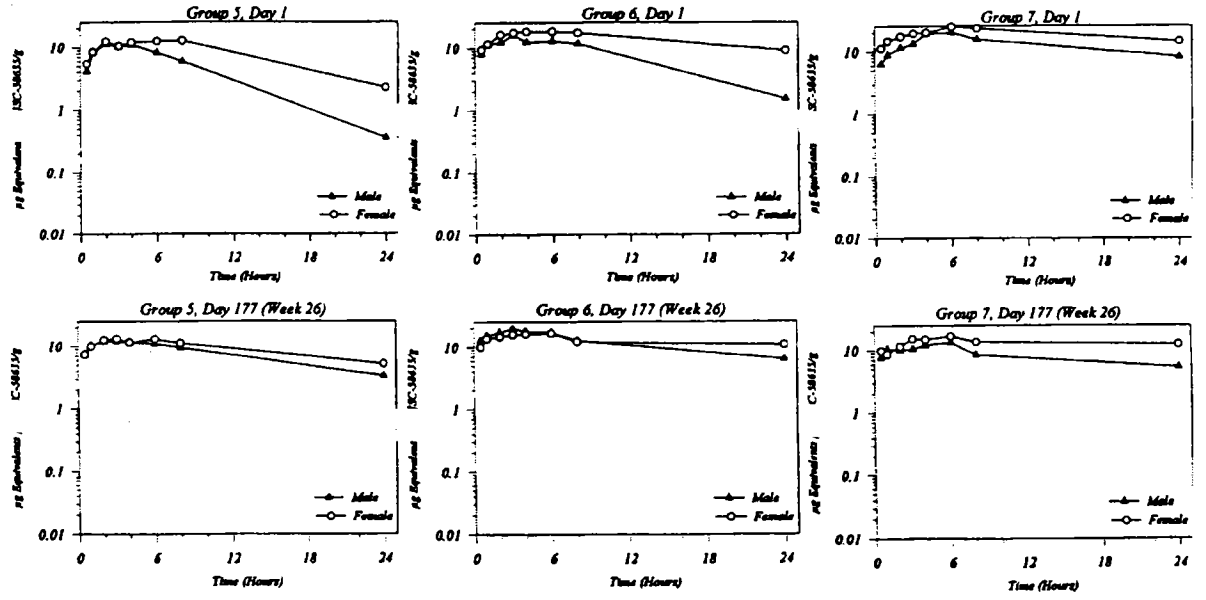


APPEARS THIS WAY ON ORIGINAL

The following table shows C_{max} and T_{max} values for radioactivity in plasma and RBC following oral administration of [ ] SC-58635 on Days 1 and 177.

Sample	PK Parameters	Sampling Day	20 mg/kg		80 mg/kg		400 mg/kg	
			♂	♀	♂	♀	♂	♀
Plasma	C_{max} (μg eq/g)	1			6.79	5.73		
		177			3.90	6.15		
	T_{max} (hr)	1			6	6		
		177			2	3		
RBC	C_{max} (μg eq/g)	1			16.1	18.2		
		177			19.7	16.3		
	T_{max} (hr)	1			3	6		
		177			3	6		

Mean concentrations of radioactivity in plasma on Days 1 and 177 for rats receiving 20, 80, and 400 mg/kg/day are shown in the following graphs.



- Excretion of Radioactivity in Urine and Feces - The primary radioactivity execration route was via feces. Mean cumulative and total percent radioactivity excreted in feces and urine during 0-168 hr following oral administration of [ ] SC-58635 on Days 1 and 177 are summarized in the following table.

Dose mg/kg	Sampling Day	Feces		Urine		Cage Rinse		Total Excretion	
		♂	♀	♂	♀	♂	♀	♂	♀
20	1								
	177								
80	1	88.5	73.5	2.12	4.35	7.69	17.2	98.6	96.2
	177	83.7	83.6	6.11	7.29	2.49	3.34	93.2	94.7
400	1								
	177								

APPEARS THIS WAY ON ORIGINAL

3.4.1.6. Effect Of SC-58635 Oral Administration On Liver Microsomal Enzyme Activities And Cytochrome P-450 Content In Male And Female Rats, Document No.: MRC-94S-0088; Date: 16-May-1995 (Vol. 1.73, 72-155)

Report Nº: MRC-94S-0088

Study Aim: (1) To examine the time course of induction by SC-58635 of its own metabolism.
(2) To evaluate the potential effect of SC-58635 on metabolism of concurrently administered drugs by determining its effects on metabolism of several in vitro substrates.

Compound: SC-58635 suspension in 1.5% methylcellulose and 0.1% Tween 80, 20 mg/ml for oral administration; SC-58635, 100,000 dpm/0.5 µl DMSO for in vitro study

Dose & Route: 200 and 400 mg/kg, po (by gavage)

Animals: 16♂ & 16♀ Sprague-Dawley rats, Crl:CD(SD)BR, 8-12 wk old, 6 and 10/sex/group

Study Location: G.D. Searle & Co, 4901 Searle Parkway, Skokie, IL 60077 & 800 N. Lindberg, St. Louis, MO 63167

Compliance with GLP/QAU: N/A

Study Design: Animal grouping, dose of administration, and sampling schedule were presented in the following table.

Group	Treatment	Dose (mg/kg)	Dose (Days)	Nº Animals	Sampling Day	
					Blood	Liver
1A	Control	0	4	3/sex	None	5
1B	Control	0	10	3/sex	None	11
2A	SC-58635	200x2	4	3/sex	5	5
2B	SC-58635	200x2	7	3/sex	8	8
2C	SC-58635	200x2	10	4/sex	2, 5, 8, 10, 11	11

Animal received the indicated dose twice per day, at 8 A.M. and 4 P.M. for 4, 7, or 10 days. Selected rats were sacrificed on days 5, 8, and 11. Plasma concentration of SC-58635 were determined for C_{max} at 3 hr post dose on days 2, 4, 8 and 10, and for C_{min} on days 5, 8, and 11 just prior to sacrifice. Liver microsomes were prepared from SC-58635 treated and control rats and analyzed for protein, cytochrome P-450 content and activity using different substrates.

Results: Treatment with SC-58635 at 400 mg/kg for 4, 7, or 10 days did not affect liver weights, liver weight/body weight ratios, or microsomal protein/g liver, but induced a significant increase in cytochrome P-450/mg microsomal protein in male rats.

The microsomal enzyme activities/mg microsomal protein which included ethoxyxoumarin o-deethylase (ECOD), p-nitroanisole o-demethylase (NADO), p-nitrophenol hydroxylase (NPH), pentoxyresorufin o-dealkylase (PROD; Day 10), testosterone 6-β hydroxylase and testosterone 16-β hydroxylase (Day 4 only) were significantly increased by SC-58635 treatment in male rats at both days 4 &10 unless otherwise indicated.

SC-58635 plasma C_{max} dropped ~60% between day 2 and day 10 in both ♂ & ♀ during repeated daily dosing. Male C_{max} appeared to be near steady state by Day 4, while female C_{max} did not reach steady state until Day 8. Mean plasma levels of SC-58635 (C_{max} & C_{min}) during daily oral administration of 400 mg/kg to both ♂ & ♀ rats are summarized in the table listed below.

Group (N)	Day	Time (hr)	SC-58635 Concentration (µg/ml)	
			♂	♀
2C (4)	2	3 (for C_{max})	9.33 ± 1.09	28.2 ± 3.3
	4		5.18 ± 0.24	21.3 ± 5.4
	8		4.15 ± 0.65	12.0 ± 1.7
	10		3.78 ± 0.17	11.1 ± 1.5
2A (3)	5	0 (for C_{min})	1.17 ± 0.26	10.1 ± 1.5
2B (3)	8		2.83 ± 1.53	11.4 ± 1.4
2C (4)	11		0.53 ± 0.05	7.74 ± 1.08

No significant increases in female microsomal enzyme activities/mg microsomal protein were observed on Day 4, but the activities of ECOD, PROD, benzyloxy resorufin o-dealkylase and testosterone 6-β and 16-β hydroxylase were increased significantly on Day 10.
CYP2B but not CYP1A, or CYP2A or CYP3A1 was demonstrated to be increased in both male and female rat microsomes by Day 4 of SC-58635 treatment.

3.4.2. MOUSE/RAT/DOG/RABBIT

3.4.2.1. The Metabolism Of SC-58635 In The Mouse, Rat, Rabbit And The Dog, Document No.: M3096266; Date: 02-Dec-1997 (Vol. 1.73, 156-207)

Report Nº: M3096266
Study Aim: To determine if the glucuronide conjugate of SC-62807 is a urinary metabolite of [ ]SC-58635 in mouse, rat, rabbit or dog. Due to the instability of glucuronide conjugates in alkaline pH 7, following the administration of [ ]SC-58635 to mouse, rat, rabbit and dog, the urine was collected at a pH of 5.0 or below to insure the stabilization of any acyl glucuronides that might be present.
Compound: [ ]SC-58635 ((Lot Nº GDS-4671-84, 141 μCi/mg) and SC-58635 (Lot Nº: 94-031-A74 & 94L-013-A1A) in the polyethylene glycol (PEG) 400:saline (2:1) at a concentration of 5 mg/ml.
Dose & Route: 5 or 10 mg/2 ml/kg iv
Animals: 3♀ Charles River CD-1 mice, weighing g
2♂ male Sprague Dawley rats, weighing g
1♂ New Zealand White rabbit, weighing 3.6 kg
1♂ pure-bred Beagle dog, weighing 11.3 kg
Study Location: G.D. Searle & Co, 4901 Searle Parkway, Skokie, IL 60077
Compliance with GLP/QAU: N/A
Urine Sampling: The urine was collected over 48 hr from the mouse, rat, rabbit and dog by free catch into containers packed in dry ice containing 0.1M sodium acetate buffer, pH 5.0 to stabilize any glucuronide conjugates that may be formed. The urine samples were thawed in an ice bath and 0.1M sodium acetate buffer, pH 5.0, was added to adjust the pH to approximately 5.0. The following table shows the sampling times and the doses for each species.

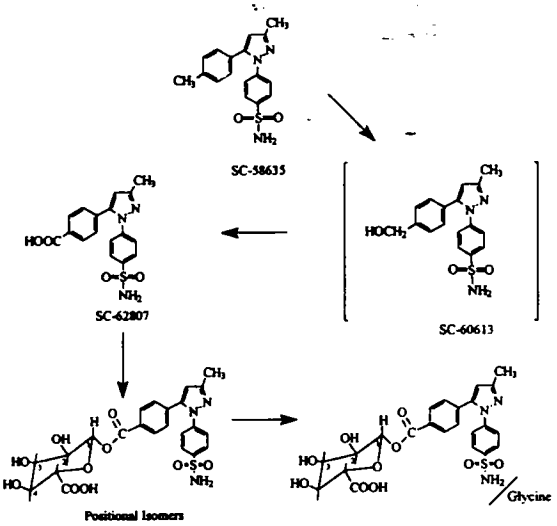
Species	Mouse	Rat	Rabbit	Dog
Dose/Route	10 mg/2 ml/kg iv	10 mg/2 ml/kg iv	5 mg/2 ml/kg iv	5 mg/2 ml/kg iv
Time of Urine Collection	0-24 & 24-48 hr	0-24 & 24-48 hr and 0-4, 4-24, and 24-48 hr	0-24 & 24-48 hr	0-4, 4-24, and 24-48 hr

Sample Determination: The distribution of radioactivity in urine from each species dosed was determined by . The identification of the metabolites in rabbit urine was confirmed by

Results: SC-58635 is metabolized through a single pathway in all species examined. The aromatic methyl group of SC-58635 is oxidized first to a hydroxyl methylene group (SC-60613) followed by complete oxidation to the carboxyl moiety (SC-62807).
Mouse - 100% of the radioactivity in the profiles of urine collected in buffer at pH 5.0 was at the same retention time as SC-62807 indicating that SC-62807 was a major urine metabolite.

Rat - Approximately 92.3% and 2.60% of the radioactivity in the profiles of urine collected in buffer at pH 5.0 was at the same retention time as SC-62807 and SC-58635, respectively. These results indicate that SC-62807 was the major urine metabolite of SC-58635 in the rat.

Rabbit - Four metabolites, SC-62807, two glucuronide conjugates and a glucuronide/glycine conjugates of SC-62807 (a dual conjugate of SC-62807), were identified in the urine by The position of the conjugation at the carboxylic acid moiety of SC-62807 was determined Data showed that the two acid glucuronide conjugates of SC-62807 were likely positional isomers generated by acyl migration. The majority (92.3%) of the radioactivity in the urine collected in buffer at pH 5.0 was SC-62807 where only a minor portion of the radioactivity (<3%) in urine were conjugates of SC-62807. The proposed metabolic pathway in rabbit urine is depicted in the right figure.



Proposed Metabolic Pathway of SC-58634 in Rabbit Urine

Dog - the majority of the radioactivity in the HPLRC profiles of urine collected in buffer at pH 5.0 was at the same retention time as authentic SC-62807, indicating that SC-62807 was the major urine metabolite of SC-58635 in the dog.

distribution of radioactivity in the urine collected after the intravenous administration of SC-58635 to the mouse, rat, rabbit and dog is enlisted in the following table.

Species (Animal #)	Dose (mg/kg)	Collection Period (Hours)	% Radioactivity 6-10.5 min	10.5-11.0 min (Tr=SC-62807)	11.0-19.5min	Present at 19.5-20min (Tr=SC-58635)
Mouse #1	12.9	0-24				
Mouse #2	9.32	0-24				
Mouse #3	12.2	0-24				
Rat	10.0	0-24				
Rat	10.0	24-48				
Rat	10.6	0-4				
Rat	10.6	4-24				
Rat	10.6	24-48				
Dog	5.24	0-4				
Dog	5.24	4-24				
Dog	5.24	24-48				
Rabbit	5.18	0-24				
Rabbit	5.18	24-48				

NA Not Analyzed

3.4.3. DOG

3.4.3.1. Preparation Of Postmitochondrial Supernatant And Microsomes From Dogs Known To Be Either Slow Or Fast Metabolizers Of SC-58635, Document No.: MRC-95S-0104; Date: 27-Nov-1995 (V0l. 1.73, p. 208-253)

Report Nº: MRC95S-0104

Study Nº: 6127-245
Study Aims: To prepare microsomes and postmitochondrial supernatants from both slow and fast metabolizer dogs and analyze for total protein and P450 content.
Study Site:
Study Date: 4/9/95 - 4/10/95
Study Design: Seven male and eight female purebred beagles previously characterized as fast or slow metabolizers of SC-58635 were sacrificed, and livers and jejunal mucosa scrapings were collected from each animal. Liver microsomes and postmitochondrial supernatants were prepared. The liver microsomes were analyzed for total P450 content and total protein. The postmitochondrial supernatant was analyzed for total protein.

Results: Approximately one quarter of each liver was used for preparation of postmitochondrial supernatant and one quarter for microsomes. The protein yields of postmitochondrial supernatants ranged from of liver and were similar regardless of the rate of clearance and sex. The protein yields of microsomes ranged from of liver in males and of protein/g of liver in females. Similar yields were obtained from dogs with either fast or slow clearance rate groups within the same sex. The total microsomal P450 content ranged from 0.384 to 0.623 nmol /mg protein and was similar for both clearance rate groups and sexes. Results from this study were similar to those in Report Nº MRC-95C-100-950295

3.4.3.2. The *In Vitro* Metabolism of SC-58635 In Rat, Human, Dog Liver S9 (A Pilot Study), Document No.: MRC-94S-0168; Date: 09-Jan-1995 (Vol. 1.73, p. 254-283)

Report Nº: MRC-94S-0168
Study Aim: To evaluate the metabolism rate of SC-58635 in vitro and the metabolic profile of SC-58635 in rat, dog and human liver S9
Compound: SC-58635, 100,000 dpm/0.5 :l DMSO
Study Location: G.D. Searle & Co, 4901 Searle Parkway, Skokie, IL 60077 & 800 N. Lindberg, St. Louis, MO 63167
Compliance with GLP/QAU: N/A
Study Design: Liver S9 fractions of ♂ & ♀ rats, dogs and humans were incubated with various concentrations of SC-58635 and an NADPH-generating system with or without UDP-glucuronic acid for the appropriate times. Reactions were terminated by the addition of formic acid to the final concentration of 2.1%. Sample were then subjected to the

Results:
K_m and V_{max} values for SC-58635 metabolism in rat, dog and human liver S9 were present in the following table.

Species	K_m (µg/ml)		V_{max} (ng/min/mg protein)	
	♂	♀	♂	♀
Rat				
Dog				
Human				

APPEARS THIS WAY
ON ORIGINAL

The data showed that male rat liver metabolized SC-58635 greater than female rats. There was a tremendous variation (7x) in the metabolic rate of SC-58635 in different human liver S9 preparations (N=7). The liver S9 preparation from one human donor did not show any metabolic activity for SC-58635.

3.4.3.3. *In Vitro* Metabolism Of SC-58635 By Dog Liver Microsomes And Cytochrome P450, Document No.: M3095157; Date: 08-Jan-1998 (V0l. 1.73, p. 284-319)

Report Nº: M3095157

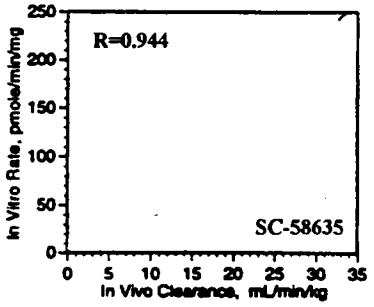
Study Aims: To establish that the slow and fast phenotypes correlate with hepatic P450 mediated metabolism and to determine which enzymes are involved.

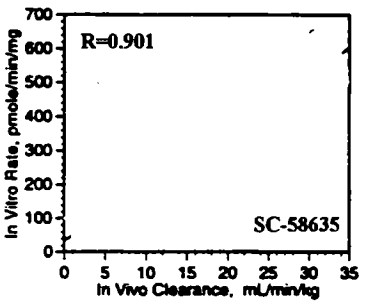
Compound: SC-58635 and [^{14}C]SC-58635

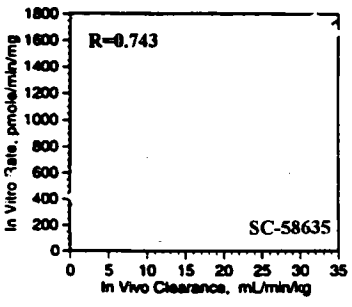
Specimens: Liver microsomes were isolated from 10 beagle dogs known to be either fast or slow metabolizers of SC-58635.

GLP/QAC Compliance: N/A

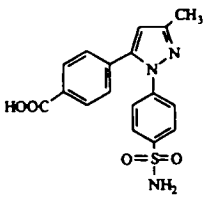
Results: The *in vitro* metabolism of SC-58635 was investigated using liver microsomes isolated from two distinct populations of beagles that were either slow or fast elimination of SC-58635 *in vivo*. Hepatic microsomes from fast SC-58635 clearance dogs metabolized this drug at a higher rate than microsomes from slow clearance dogs. Correlation analysis of *in vitro* metabolism rates with in vivo clearance rates (N=20 dogs) showed that correlation coefficients (r) were of 0.944, 0.901 and 0.743 at in vitro SC-58635 substrate concentrations of 2.6, 10 and 100 μM (1.0. 3.8 and 38 μg/ml), respectively as shown in below figures.



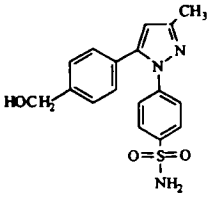




The major metabolites of SC-58635 generated by dog liver microsomes were SC-60613 and SC-62807 which are the same as the major (unconjugated) metabolites *in vivo*. The *in vitro* metabolism of SC-65872 was NADPH-dependent, and was prohibited by carbon monoxide (CO), an inhibitor of cytochrome P450 (CYP) enzymes. Separate studies showed that human recombinant CYP2C9, CYP2C19 and CYP3A4 but not CYP2D6 metabolized SC-58635 and CYP2C9 was responsible for the major portion of SC-58635 metabolism by human liver microsomes. A series experiment with recombinant canine P450 isozymes to determine which isozymes contribute to SC-58635 metabolism showed that isoforms in the CYP2D subfamily had high activity for the oxidative metabolism of SC-58635, whereas CYP2B11, CYP2C21 and CYP3A12 had low activities activity for the oxidative metabolism of SC-58635. Bufuralol, a putative marker substrate for CYP2D, was readily metabolized by 4 CYP2D15 isoforms and to lesser extent by CYP2B11, CYP2C21 and CYP3A12. Bufuralol hydroxylase activity was highly correlated (r=0.961) with SC-58635 metabolism with recombinant protein. Furthermore, microsomes from both fast and slow dogs were significantly inhibited by quinidine, a potent CYP2D inhibitor. Altogether, these results suggest CYP2D15 is the major P450 responsible for SC-58635 metabolism in the dog. The complexity of the canine CYP2D15 system, with the presence of several variants, might be attributable to the differences in the rate of SC-58635 metabolism in the populations of slow and fast dogs.



SC-62807



SC-60613

3.4.3.4. Analysis Of Plasma, Urine And Fecal Samples From Dogs Dosed With]SC-58635 During A 4-Week Oral Toxicity Study Of SC-58635 In The Dog (SA4260), Document No.: MRC-94S-0144; Date: 29-Nov-1994 (Vol. 1.74, p. 1-125)

Study Nº: SA4260
Report Nº: PSA-94S-0144
Study Aim: To determine absorption of the test article, the relationship of plasma concentrations of SC-58635 with dosage and duration of dosing, the metabolism of SC-58635 and evidence for sex-related differences in any pharmacokinetic parameters.
Compound: SC-58553 (Lot Nº 94K014-A1B) and [^{14}C]SC-58635 (38.4 μCi/mg) in gelatin capsule
Dose & Route: 20, 25, 50, 100 and 250 mg/kg/day in gelatin capsule po
Animals: ♂ & ♀ beagle dogs, months old, weighing kg, 4 or 8/sex/group
Study Location: G.D. Searle, Skokie, IL
Compliance with GLP/QAU: No
Study Design: SC-58635 was administered orally in a gelatin capsule to dogs at a dose of 25 mg SC-58635/kg/day for 28 days and at a dose of 100 mg SC-58635 /kg/day for 15 days (Groups 6 and 7). SC-58635 was administered on Days 1 and 28 to the dogs @ 25 mg/kg (Group 6) and on Days 1 and 15 to the dogs @ 100 mg/kg (Group 7). The dogs were dosed with unlabelled SC-58635 on the intervening days. Blood was collected at 0.5, 1, 1.5, 2, 2.5, 3.5, 5, 7, and 24 hr on Days 1 and 15 from dogs @ 100 mg/kg group or on Day 28 from dogs @ 25 mg/kg. Urine and feces were collected over a 7 days period (-18-0, 0-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hr) following dosing with SC-58635. Urine was collected by free-catch in containers surrounded by dry ice and feces were collected into bags. Whole blood, plasma, red blood cells, urine and feces were analyzed for by a method. The concentrations of SC-58635 in plasma were determined using a validated procedure. The metabolic profiles of selected plasma, urine and fecal samples were determined using a e.

Group		Dose (mg/kg)	Nº Animals /Sex/Group	Nº Animals/Sex Sacrificed	
				Day 17	Days 29-31
Toxicology Study	1	0	4 (4)*	-	8
	2	25	4	-	4
	3	50	4	-	4
	4	100	4 (4)*	4	4
	5	250	4 (4)*	4	4
PK Study**	6	25	2		
	7	100	2		

* The number in the parenthesis indicating the number of animals were used in the 2 week reversal phase study.
** Animals in group 6 & 7 were treated with]SC-58635.

APPEARS THIS WAY ON ORIGINAL

Results: One female dog in Group 7 (100 mg/kg) was moribund and sacrificed on Day 12. This animal was not given a second dose of radiolabeled SC-58635 and a single 0 hour blood sample was collected for analysis for SC-58635.

- Concentrations in Plasma, Red Blood Cells and Whole Blood PK Parameters - SC-58635 was absorbed and systemically available. The exposures to SC-58635 increased with dose. Accumulation of SC-58635 might have occurred as higher C_{max} and AUC values were noted on Day 28. The mean Cmax and AUC values for SC-58635 were higher in female dogs than male dogs.

SC-58635 Concentration (μg eq/ ml)								
Time (hr)	25 mg/ kg				100 mg/ kg			
	Day 1		Day 28		Day 1		Day 15	
	♂	♀	♂	♀	♂	♀	♂	♀
PLASMA								
0.5								
1								
1.5								
2								
2.5								
3.5								
5								
7								
24								
RBC								
0.5								
1								
1.5								
2								
2.5								
3.5								
5								
7								
24								
WHOLE BLOOD								
0.5								
1								
1.5								
2								
2.5								
3.5								
5								
7								
24								
PK PARAMETERS								
T_{max} (hr)	1.5	1.5	2	5	24	7	2	2.5
C_{max} (μg eq/ml)								
AUC_{0-24} (μg eq•hr/ml)								

- Plasma SC-58635 PK Parameters -

PK Parameters	25 mg/kg				100 mg/kg			
	Day 1		Day 28		Day1		Day 15	
	♂	♀	♂	♀	♂	♀	♂	♀
Tmax (hr)	1.5	1.25	2	3.25	13.75	6	1.5	2
Cmax (μg/ml)								
AUC0-24 (μg•hr/ml)								

- Metabolic Profiles in Plasma - analysis showed that SC-58635 was the major circulating compound for both ♂ and ♀ @ 25 or 100 mg/kg on Days 1, 15 or 28 of dosing.
- Metabolite Profiles in Feces -

Metabolites (%)	Mean (± SEM) % Dose Excreted in Feces							
	25 mg/kg				100 mg/kg			
	Day 1		Day 28		Day 1		Day 15	
	0-24 hr	24-48 hr	0-24 hr	24-48 hr	0-24 hr	24-48 hr	0-24 hr	24-48 hr
SC-58635	72.6 ± 2.0	0.54 ± 0.45	58.0 ± 14.8	0.86 ± 0.43	39.1 ± 14.8	14.7 ± 14.5	60.1 ± 5.7	11.3 ± 6.92
SC-60613	NP	NP	NP	NP	NP	NP	NP	NP
SC-62807	13.65 ± 5.2	5.94 ± 0.33	17.8 ± 6.7	18.9 ± 7.3	11.7 ± 2.9	32.4 ± 14.5	4.19 ± 2.21	8.28 ± 7.3

NP = No peak present in profile in the SC-60613 position.

- Metabolic Profiles in Urine -

Metabolites (%)	Mean (± SEM) % Dose Excreted in Urine (0-24 hr)			
	25 mg/kg		100 mg/kg	
	Day 1	Day 28	Day 1	Day 15
SC-58635	0.00482 ± 0.00280	0.00157 ± 0.00157	0.00196 ± 0.00196	0.0122 ± 0.0122
SC-60613	NP	NP	NP	NP
SC-62807	0.416 ± 0.114	0.662 ± 0.227	0.812 ± 0.313	0.635 ± 0.398
M1[a]	0.0142 ± 0.00442	0.0321 ± 0.0156	0.0383 ± 0.0125	0.0374 ± 0.0217

NP = No peak present in profile in the SC-60613 position.

[a] Radioactivity eluted as a position between [14C]SC-58635 and [14C]SC-62807.

- Total in Urinary and Fecal Excretion - The majority (greater 90%) of the recovered dose was excreted in the feces as]SC-58635 and SC-62807 as shown in the following table.

Sample	Mean Cumulated (0-168 hr) % Radioactive Dose in Feces and Urine							
	25 mg/kg				100 mg/kg			
	Day 1		Day 28		Day 1		Day 15	
	♂	♀	♂	♀	♂	♀	♂	♀
Urine	0.523	0.979	0.525	2.71	2.20	5.63	1.38	2.82
Feces	85.5	103.5	99.7	101	116	102	85.9	97.3
Total	86.1	104	100	104	119	108	87	100

3.4.3.5. Metabolism Support For A 13-Week Capsule Toxicity Study With SC-58635 In Dogs, SA4324, Document No.: MRC95S-30-950263; Date: 27-Nov-1995 (V0l. 1.74, p. 126-193)

Report Nº: MRC95S-30-950263

Study Nº: 6127-233/SA4324

Study Aim: To determine PK, metabolism and excretion of SC-58635 during a 13-week oral capsule toxicity study in dogs.

Compound: SC-58635 (Lot Nº 94K014-A2B) and SC-58635 (Lot Nº GDS 4404-164, 2.13 μCi/mg & GDS 4404-165, 1.07 μCi/mg) in gelatin capsule

Vehicle: Empty gelatin capsule

Dosage: 0, 15, 25, and 35 mg/kg/day po for ≥13 weeks

Animals: 30♂ & 30♀ beagle dogs, months old. Weighing kg

Main and Recovery[a] Study				Satellite PK Study			
Group	Dose (mg/kg/dose)	Dose (mg/kg/day)	Nº of Animals	Group	Dose (mg/kg/dose)	Dose (mg/kg/day)	Nº of Animals
1[a]	0	0	6/sex[c]	6[a,b]	7.5	15	3/sex
2[a]	7.5	15	4/sex	7[a,b]	12.5	25	3/sex
3[a]	12.5	25	4/sex	[a]Animals in Group 1-4, 6 and 7 were dosed twice daily at 12-hr intervals for ≥13 weeks.			
4[a]	17.5	35	6/sex[c]	[b]Two animals/sex in group 1, 4, and 5 had a recovery phase for 28 days after a 13-week treatment.			
5	25	25	4/sex[c]	[c]Animals in group 6 and 7 received [14C]SC-58635 at the first daily dose on day 1 and once during weeks 6 and 13.			

Study Location:

G.D. Searle, Skokie, IL

Study Date: March 10, 1995 - July 10, 1995

Compliance with GLP/QAU: Yes

Study Design: Three dogs /sex/group were administered SC-58635 at a dose level of 7.5 or 12.5 mg/kg bid for 13 weeks. A single dose of [^{14}C]SC-58635 was administered on Days 1, 39 (Week 6) and 87 (Week 13) and nonradiolabeled SC-58635 was given in the intervening days. Blood samples

were collected at 30 min, 1, 2, 3, 5, 7, 12, 13, 14, 15, 18, and 24 hr post dose on Days 1, 39 and 88 for radioactivity determination. Urine and feces were collected at 24 hour intervals through 168 hours after each radiolabeled dose. Post-mitochondrial supernatant fractions and microsomes were prepared from the liver samples from selected animals in Group 1 (control), Group 2 (15 mg/kg/day), Group 3 (25 mg/kg/day), Group 4 (35 mg/kg/day) and Group 5 (25 mg/kg/day). Whole blood, plasma, red blood cells, urine and feces were analyzed for by a method. The concentrations of SC-58635 in plasma were determined using a validated procedure. The metabolic profiles of selected plasma, urine and fecal samples were determined using procedure.

Results: In this report, the results of the profiles of plasma, urine and fecal samples and in vitro incubations of liver microsomes were presented.
The majority of the radioactivity circulating in plasma was SC-58635 with values ranging from SC-60613, the hydroxylated metabolite of SC-58635, also circulated in plasma, but at lower levels . The metabolic profile of SC-58635 in plasma differed in dogs characterized as having fast and slow SC-58635 clearances. Higher plasma levels of SC-60613 were found in fast SC-58635 clearance dogs than dogs with a slow SC-58635 clearance. The majority of the urine (0-48 hr) radioactivity was excreted as SC-62807. SC-58635 was also excreted in urine (0-48 hours), but at low levels on Days 1 and 39. No parent compound was excreted in urine on Day 88. There were no differences between sex and dose in the urine excretion profile.
The majority of the radioactivity excreted in the feces was SC-58635 and SC-62807. There were no differences between sex, dose or duration of dosing in the fecal excretion profile. The following table shows mean (±SEM) percent of dose excreted in feces (0-72 hours) as SC-58635 and SC-62807 during Weeks 1, 6 and 13 in ♂ and ♀ dogs or in dogs characterized as having a fast or slow SC-58635 clearance.

Week	% of dose excreted as SC-58635				% of dose excreted as SC SC-62807			
	7.5 mg/kg bid		12.5 mg/kg bid		7.5 mg/kg bid		12.5 mg/kg bid	
	♂	♀	♂	♀	♂	♀	♂	♀
1	75.6 ± 9.9	87.1 ± 3.8	77.4 ± 4.6	62.6 ± 13.6	19.4 ± 9.5	17.1 ± 10.8	11.5 ± 0.7	27.9 ± 13.9
6	65.6 ± 12.0	69.7 ± 12.5	75.8 ± 2.7	68.4 ± 9.5	24.0 ± 9.6	22. 3 ± 12.2	14.6 ± 2.8	25.6 ± 17.2
13	78.2 ± 11.5	70.5 ± 7.8	77.3 ± 12.7	63 .7 ± 10.4	15.6 ± 10.4	19.9 ± 7.6	14.3 ± 11.1	26.1 ± 9. 9
	Fast	Slow	Fast	Slow	Fast	Slow	Fast	Slow
1	78.0 ± 11.5	84 .7 ± 1.63	82.9 ± 1.0	57.1 ± 9.7	26.7 ± 10.8	9.78 ± 4.4	10.3 ± 1.5	29 .2 ± 13.0
6	68.9 ± 13.2	66.4 ± 11.2	75.5 ± 2.6	68.8 ± 9 .7	20.9 ± 10.8	25.4 ± 10.9	13.7 ± 3.4	26.5 ± 16.8
13	70 .7 ± 7.7	78.0 ± 11.7	68.9 ± 12.0	72.0 ± 13.0	20.6 ± 8.2	14.9 ± 9.7	21.4 ± 10.5	19.1 ± 12.0

Mean (±SEM) percent of SC-58635 and SC-60613 in dog liver microsomes from ♂ and ♀ dogs or from dogs characterized as having fast or slow SC-58635 clearance incubated with SC-58635 are tabulated as follows. The percentage of SC-58635 converted to SC-60613 was greater in liver microsomes from dogs characterized as having a fast SC-58635 clearance than in liver microsomes from dogs characterized as having a slow SC-58635 clearance.

Dose (mg/kg/day)	% SC SC-62813				% SC-58635			
	♂	♀	Fast	Slow	♂	♀	Fast	Slow
Control	14.6 ± 4.4	14.0 ± 1.4	16.1 ± 2.5	9.00	71.3 ± 6.0	78.1 ± 1.7	73.7 ± 4.0	77.7
15	15.5 ± 5.3	14.8 ± 4.6	22.4 ± 3.7	7.88 ± 0.62	77.9 ± 5.7	84.5 ± 4.7	73.7 ± 4.3	88.7 ± 2.1
30	19.7 ± 6.7	10.8 ± 1.2	22.1 ± 5.3	8.45 ± 0.28	79.6 ± 6.7	88.9 ± 1.2	77.4 ± 5.4	91.2 ± 0.3

3.4.3.6. Metabolism Support For A 52-Week Capsule Toxicity Study With SC-58635 In Dogs, SA4425, Document No.: M3097112; Date: 17-Jun-1997 (Vol. 1.74, p. 194-225)

Study Nº: 700-338/SA4425
Report Nº: M3097112

Study Aim: To determine the metabolic profiles in plasma, urine and feces.
Compound: SC-58635 (Lot Nº 94K014-A2B); SC-58635 (Lot Nº GDS 4671-90, 2.08 μCi/mg)
Vehicle: Empty gelatin capsule
Dosage: 0, 15, 25, and 35 mg/kg/day po for 52 weeks
Animals: 56 & 56 beagle dogs, ~7 months old, weighing kg for the ♂ and kg for the ♀.

Main and Recovery Study				Satellite PK Study			
Group	Dose (mg/kg/dose)	Dose (mg/kg/day)	Nº of Animals/Sex	Group	Dose (mg/kg/dose)	Dose (mg/kg/day)	Nº of Animals/Sex
1	0	0	12	6	7.5	15	4
2	7.5	15	8	7	17.5	35	4
3	12.5	25	8	4/sex from Groups 1-5 were sacrificed at Week 26.			
4	17.5	35	12	Dogs in Groups 1-4 & 6-7 received SC-58635 2x/day.			
5	25.0	25	8	Dogs in Groups 6 & 7 received [^{14}C]SC-58635 as 1st daily dose on Day1 and Weeks 26 and 52.			

Study Location: G. D. Searle, Skokie, IL for metabolic profile determination.
Compliance with GLP/QAU: Yes
Experimental Design:
Dogs were given SC-58635, 0, 7.5x2, 12.5x2, 17.5x2 or 25x1 mg/kg/day in gelatin capsule orally gavage for at least 52 weeks; dosing continued through the day before terminal sacrifice (Weeks 52). Recovery animals were kept without treatment for an additional 4 weeks. Dogs in the companion PK study group received SC-58635 on Day 1, and Weeks 26 (Day 176) & 52 (Day 358) and received nonradiolabeled SC-58635 on other days during the study. Blood samples were collected at 0.5, 1, 2, 3, 4, 5, 7, 12, 13, 14, 15, 18 and 24 hr following the ingestion of radiolabeled SC-58635. Urine and fecal samples were collected for 168 hr after each radiolabeled dose approximate 24-hr intervals. Necropsies were performed on all animals at the end of the study. The metabolic profiles of selected plasma, urine and fecal samples were determined using a procedure.

Results: This report summarized the metabolic profile data from plasma, urine, and feces. The majority of the radioactivity circulating in plasma samples collected 4 and 18 hours post radiolabel dose administration on Days 1, 176 and 358 was parent drug. The hydroxyl, SC-60613, and carboxyl, SC-62807, metabolites of SC-58635, also circulated in plasma at lower levels. Group 7 dogs with a fast SC-58635 clearance had ≥75% of SC-60613 in the circulation at Week 52. The following table presents the percent of SC-58635, SC-62807 and SC-60613 in profiles of pooled plasma samples.

APPEARS THIS WAY
ON ORIGINAL

Group	Week	Time hr	% SC-58635				% SC-60613				% SC-62807			
			slow		fast		slow		fast		slow		fast	
			♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
6	1	4	87.2	100 d	98.5	a	12.8	b, d	1.50	a	b	b, d	b	a
7	1	4	87.1	100 c	69.0 c	68.0	12.9	b, c	31.0 c	28.8	b	b, c	b, c	3.21
6	1	18	100 d	100 d	95.6	a	b, d	b, d	4.39	a	b, d	b, d	b	a
7	1	18	50.7 d	a	100 d	a	49.3 d	a	b, d	a	b, d	a	b, d	a
6	26	4	61.0 d	98.1 d	100 d	53.8 d	b, d	1.94 d	b, d	40.0 d	b, d	b, d	b, d	6.15 d
7	26	4	78.3 c	100c	100 d	65.6 d	21.7 c	b, c	b, d	34.4 d	b, c	b, c	b, d	b, d
6	26	18	91.0	100	100 d	100 d	9.03	b, d	b, d	b, d	b	b, d	b, d	b, d
7	26	18	93.4	100 d	100 c	a	6.56	b, d	b, c	a	b	b, d	b, c	a
6	52	4	100 d	a	a	75.0 d	b, d	a	a	25.0 d	b, d	a	a	b, d
7	52	4	100 c	78.0	86.8 c	74.5	b, c	14.4	13.2 c	16.7	b, c	7.68	b, c	8.79
6	52	18	74.2	a	a	78.1	7.59	a	a	4.14	15.1	a	a	17.8
7	52	18	48.2	62.1	12.2	23.2	46.0	36.7	83.6	76.8	2.20	b	1.31	b

[a] Plasma samples with radioactivity levels less than 1000 DPM/ml were not analyzed.
[b] No peak detected.
[c] The amount of radioactivity injected
[d] The amount of radioactivity injected

Due to < 2% of the dose was excreted in urine from 0 - 168 hours, urine samples were not profiled by The radioactivity excreted in the feces was mostly SC-58635 and SC-62807 with the mean percent of dose excreted 0 - 72 hr post-dose ranging from , and respectively. The % of dose excreted in pooled fecal homogenates (0-72 hr) as SC-58635 and SC-62807 on Weeks 1, 26 and 52 in dogs characterized as having a fast or slow SC-58635 clearance are shown in the following table.

Group	Week	% of dose excreted as SC-58635				% of dose excreted as SC-62807			
		Fast SC-58635 Clearance		Slow SC-58635 Clearance		Fast SC-58635 Clearance		Slow SC-58635 Clearance	
		♂	♀	♂	♀	♂	♀	♂	♀
6	1	64.4	27.9	46.3	24.6	22.4	59.0	38.1	62.8
7	1	43.5	41.7	72.9	45.2	45.9	131	15.8	45.7
6	26	71.2	81.1	43.1	83.1	18.3	9.95	41.9	8.00
7	26	68.4	55.8	42.9	84.9	14.4	7.19	38.9	5.85
6	52	82.3	73.6	64.4	79.6	5.84	15.1	22.8	11.4
7	52	69.4	38.5	67.4	69.8	20.5	46.6	17.8	17.0

3.4.4. HUMAN IN VITRO

3.4.4.1. *In Vitro* Metabolism Of Celecoxib (SC-58635) By Human Liver Microsomes And Cytochrome P450, Document No.: M3095130; Date: 26-Feb-1998 (Vol. 1.74, p. 226-257)

The *in vitro* metabolism of Celecoxib was Investigated using human liver microsomes and cDNA-expressed human cytochrome P450 enzymes.

Results:

- The major metabolites, SC-60613 and SC-62807, of celecoxib generated by human liver microsomes were similar to the major unconjugated metabolites found *in vivo*. The apparent K_m ($K_{m(app)}$) for celecoxib metabolism by a pool of human liver microsomes was 49.3 μM (~18.8 μg/ml).
- Human recombinant CYP2C9, CY152C19, and CYP3A4 but not CYP1A2, CYP2A6, CYP21B6, CYP2D6, CYP2E1 and CYP3A5 were able to metabolize celecoxib to [^{14}C]SC-60613 in vitro.
- Results from the comparison analysis of specific enzymatic activities for celecoxib metabolism by human microsome samples (N=16) with the known (phenotyped) specific

enzymatic activities of the same microsomes for a series of cytochrome P450 isoform specific substrates are shown in the following table.

P450 Isoform (Substrate)	Celecoxib @ 2.6 μM		Celecoxib @ 10 μM	
	Regression (r^2)	Correlation (r)	Regression (r^2)	Correlation (r)
CYP1A2 (Ethoxyresorufin)	0.315*	-0.561	0.223	-0.472
CYP2A6 (Ethoxycoumarin)	0.078	0.279	0.018	0.135
CYP2C9 (Tolbutamide)	0.616**	0.785	0.560**	0.748
CYP2C19 (Mephenytoin)	0.005	0.072	0.005	0.069
CYP2D6 (Bufuralol)	0.010	0.102	0.051	-0.225
CYP2E1 (Chlorzoxazone)	0.093	0.305	0.326*	0.571
CYP3A4/5 (Testosterone)	0.259*	0.509	0.186	0.432
CYP3A4 (Dextromethorphan)	0.253*	0.503	0.137	0.370
CYP4A9/11 (Lauric Acid)	0.021	-0.143	0.114	-0.338

*p≤0.05;**p≤0.001

- In addition, sulfaphenazole, a potent and specific CYP2C9 inhibitor, inhibited both celecoxib and tolbutamide to the same extent in a series of individual human microsome samples.

Therefore, human recombinant CYP2C9, CYP3A4, and CYP2C19 were capable of metabolizing celecoxib. CYP2C9 was found to be most important in human metabolism of celecoxib based on correlation analysis using a series of characterized human microsome samples, and by the effect of isoform-specific inhibitors of P450 metabolism *in vitro*.

3.4.4.2. *In Vitro* Inhibition Of Cytochrome P450 Marker Activities In Human Liver Microsomes By Celecoxib (SC-58635): Determination Of Potential For Drug-Drug Interaction, Document No.: M3097243; Date: 13-Feb-1998 (Vol. 1.74, p. 258-301)

This study was to examine the ability of SC58635 to inhibit cytochrome P450 (CYP) isoform specific catalytic activities associated with CYP2C9, CYP2C19, CYP2D6 and CYP3A4. *In vitro* interactions were conducted by incubating marker substrates with human liver microsomes in the presence of SC58635 or CYP isoform-selective chemical inhibitors to furnish initial predictive information on the potential for drug-drug interactions.

Results: The following table shows the inhibitory effects of celecoxib (SC-58635) and selective CYP inhibitors on the CYP isoenzyme activities expressed as K_i values.

P450 Isoforms	Marker	K_i (μM)				
		Celecoxib	sulfaphenazole	omeprazole	quinidine	ketoconazole
CYP2C9	tolbutamide 4-hydroxylation	44.4	0.585	-	-	-
CYP2C19	(S)-mephenytoin 4'-hydroxylation	17.8	-	5.64	-	-
CYP2D6	(±)-bufuralol 1'-hydroxylation	4.19	-	-	0.466	-
CYP3A4	testosterone 6β-hydroxylation	106	-	-	-	0.0483

Based on the data presented, celecoxib was not a potent *in vitro* inhibitor of CYP2C9, CYP2C19 or CYP3A4, and had little effect on the metabolism of substrates mediated by these cytochrome P450s.

3.4.4.3. In Vitro Metabolism Of Celecoxib By Human Liver Microsomes: Determination Of Potential For Pharmacokinetic Interactions Between Celecoxib And Glyburide, Document No.: M3096335, Date: 27-Feb-1998 (Vol. 1.74, p. 302-336)

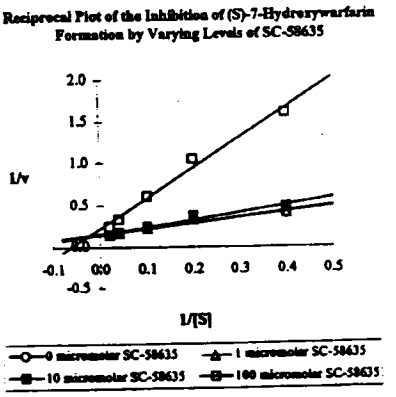
In vitro metabolism of Celecoxib and glyburide by human liver microsomes was determined. Glyburide metabolism by human recombinant CYP2C9, CYP2C19, CYP2D6 and CYP3A4, and the effect of celecoxib on this metabolism, was also determined.

Results:

- At concentrations of , the rate of glyburide metabolism by human liver microsomes was approximately linear, indicating the human microsomal apparent K_m ($K_{m(app)}$) for glyburide was > 1.25 μg/ml.
- At the highest concentration, 10 μg/ml, celecoxib inhibited glyburide metabolism by 24%, indicating that celecoxib was a weak noncompetitive inhibitor of glyburide metabolism. Glyburide was readily metabolized by human recombinant CYP3A4, CYP2C19, but not by CYP2C9 or CYP2D6. Metabolism of glyburide by recombinant human CYP3A4 in Sf9 microsomes was inhibited by celecoxib.
- Glyburide had little or no effect on human microsomal metabolism of celecoxib).The apparent K_m for celecoxib metabolism by the human liver microsomes was 7.29 μg/ml (19.1 μM).

3.4.4.4. In Vitro Drug-Drug Interaction Of SC-58635 And Warfarin
Document No.: M2097288; Date: 18-Sep-1997 (Vol. 1.74, p. 337-357)

Report Nº: M2097288
Study Aims: To identify potential clinically significant drug-drug interactions of SC-58635 with warfarin using pooled human microsomes.
Compound: (S)-Warfarin, 2.5, 5, 10, 25, and 50 μM; SC 58635, 0, 1.0, 10, and 100 μM.
Study Site:
GLP/AUC Compliance: Yes
Study Design: The metabolism of SC-58635 was shown to be mediated in part by CYP2C9 (see 3.4.4.1: Report Nº M3095130), which metabolizes warfarin to 7-hydroxywarfarin. Warfarin, at levels of 2.5, 5, 10, 25, and 50 μM, was incubated with pooled human microsomes (0.5-1.0 mg protein) in the presence of SC-58635, 0, 1.0, 10, and 100 μM. Both the depletion of racemic warfarin and the formation of (S)-7-hydroxywarfarin *in vitro* were measured. Warfarin and 7-hydroxywarfarin in *in vitro* buffer were extracted and analyzed



Results: Increasing concentrations of SC-58635 had increasing effect on the disappearance of warfarin and formation of 7-hydroywarfarin with an apparent K_i value of 21.6 μM as illustrated in the figure.

3.5. EXCRETION PATTERN

3.5.1. DOG

3.5.1.1. Evaluation Of The Total Analyses And Liver Microsomal And Postmitochondrial Supernatant Preparation In A 13-Week Capsule Toxicity Study With SC-58635 In Dogs (SA4324), Document No.: MRC95C-30-950253; Date: 27-Nov-1995 (Vol. 1.75, p. 1-130)

Study Nº: 6127-233/SA4324
Study Aim: To obtain information on the absorption and excretion of the radiolabeled test material, determine the relationship of plasma and erythrocyte concentrations of the radiolabeled test material with dosage and duration of dosing, and evaluate evidence for sex-related differences in the absorption and elimination data.

Compound: SC-58635 (Lot Nº 94K014-A2B) and SC-58635 (Lot Nº GDS 4404-164, 2.13 μCi/mg & GDS 4404-165, 1.07 μCi/mg) in gelatin capsule

Vehicle: Empty gelatin capsule

Dosage: 0, 15, 25, and 35 mg/kg/day po for ≥13 weeks

Animals: 30♂ & 30♀ beagle dogs, months old. Weighing kg

Main and Recovery[a] Study				Satellite PK Study			
Group	Dose (mg/kg/dose)	Dose (mg/kg/day)	m of Animals/Sex	Group	Dose (mg/kg/dose)	Dose (mg/kg/day)	Nº of Animals
1[a]	0	0	6[c]	6[a,b]	7.5	15	3
2[a]	7.5	15	4	7[a,b]	12.5	25	3
3[a]	12.5	25	4	[a]Animals in Group 1-4, 6 and 7 were dosed twice daily at 12-hr intervals for ≥13 weeks.			
4[a]	17.5	35	6[c]	[b]Two animals/sex in group 1, 4, and 5 had a recovery phase for 28 days after a 13-week treatment.			
5	25	25	4[c]	[c]Animals in group 6 and 7 received SC-58635 at the first daily dose on Day 1 and once during weeks 6 and 13.			

Study Location:

Study Date: March 10, 1995 - July 10, 1995

Compliance with GLP/QAU: Yes

Study Design: Three dogs /sex/group were administered SC-58635 at a dose level of 7.5 or 12.5 mg/kg bid for 13 weeks. A single dose of SC-58635 was administered on Days 1, 39 (Week 6) and 87 (Week 13) and nonradiolabeled SC-58635 was given in the intervening days. Blood samples were collected at 30 min, 1, 2, 3, 5, 7, 12, 13, 14, 15, 18, and 24 hr post dose on Days 1, 39 and 88 for radioactivity determination. Urine and feces were collected at 24 hour intervals through 168 hours after each radiolabeled dose. Microsomes and postmitochondrial supernatants were prepared from liver samples from selected animals in Groups 1-5 and analyzed to determine total protein concentrations and cytochrome P450 enzyme content.

Results: This report contained the results of the radioanalytical portion of this study, liver microsome and postmitochondrial supernatant preparation, results of microsomal analysis for total protein and cytochrome P450 enzyme concentrations, and analysis of the postmitochondrial supernatant for total protein concentration. Following oral administration of SC-58635 to male and female dogs at dose levels of 7.5 and 12.5 mg/kg, individual plasma and erythrocyte total radioactivity concentrations were highly variable which could be attributed to polymorphism in the metabolism of SC-58635. Double peak concentrations were observed in plasma and erythrocyte total radioactivity concentrations-time profiles. The first peak occurred between 1 and 5 hours, and the second peak occurred between 12 and 24 hours. Erythrocyte concentrations were ~2x of the plasma concentrations, an indicative of high partitioning into erythrocytes. The following table shows mean (±SD) C_{max} , T_{max}, and AUC_{0-t} radioactivity in plasma and RBC on Say 1 and during Weeks 6 and 13 after a single oral dose of SC-58635. C_{max} values appeared to be higher in females, this difference might be as the result of differences in the rate of elimination by fast and slow metabolizers.

	Dose mg/kg	PK Parameters	Day 1		Week 6		Week 13	
			♂	♀	♂	♀	♂	♀
Plasma	7.5	C_{max} (μg eq/ml)	0.370 ± 0.180	0.226 ± 0.099	0.331 ± 0.188	0.311 ± 0.293	0.248 ± 0.118	0.338 ± 0.319
		T_{max} (hr)	5.7 ± 5.5	12.7 ± 9.2	9.7 ± 6.7	6.0 ± 6.1	5.7 ± 6.4	5.7 ± 6.4
		AUC_{0-t} (μg eq•hr/ml)	3.40 ± 1.96	1.87 ± 1.07	3.32 ± 1.35	3.16 ± 3.22	2.19 ± 1.38	3.30 ± 3.43
	12.5	C_{max} (μg eq/ml)	0.390 ± 0.242	1.14 ± 0.902	0.212 ± 0.032	0.812 ± 0.834	0.270 ± 0.164	0.851 ± 0.412
		T_{max} (hr)	9.3 ± 5.5	4.0 ± 1.7	7.0 ± 5.3	10.0 ± 6.1	5.0 ± 6.1	9.7 ± 6.7
		AUC_{0-t} (μg eq•hr/ml)	4.42 ± 4.38	10.0 ± 8.55	2.52 ± 1.09	7.98 ± 8.28	2.26 ± 1.85	7.63 ± 5.41
RBC	7.5	C_{max} (μg eq/ml)	0.768 ± 0.362	0.504 ± 0.114	0.677 ± 0.529	0.659 ± 0.531	0.521 ± 0.367	0.727± 0.570
		T_{max} (hr)	5.7 ± 5.5	12.7 ± 9.2	9.7 ± 6.7	6.0 ± 6.1	5.7 ± 6.4	13.0 ± 11.0
		AUC_{0-t} (μg eq•hr/ml)	7.78 ± 5.14	4.87 ± 3.71	7.16 ± 4.33	6.22 ± 5.29	5.09 ± 4.26	6.70 ± 5.86
	12.5	C_{max} (μg eq/ml)	0.440 ± 2.53	2.73 ± 0.774	0.066 ± 0.619	1.38 ± 1.17	0.664 ± 0.465	1.61 ± 0.825
		T_{max} (hr)	5.9 ± 5	4.3 ± 1.2	5.3 ± 13	9.7 ± 5.8	5.0 ± 6.1	9.7 ± 5.8
		AUC_{0-t} (μg eq•hr/ml)	7.35 ± 3.54	19.5 ± 15.2	1.80 ± 4.37	13.9 ± 13.1	4.99 ± 4.06	14 .4 ± 8.46

Summary of C_{max}, T_{max}, and AUC of plasma and erythrocyte radioactivity concentrations following a single oral dose of ']SC-58635 on Day 1, and During Weeks 6 and 13 of a 13-week dosing regimen in dogs classified as fast or slow metabolizers of SC-58635 are showed in the following table. Plasma AUC values were higher in slow metabolizers compared to the fast metabolizers at both the 7.5 and 12.5 mg/kg dose levels on Day 1, and during Weeks 6 and 13.

Sample	Dose mg/kg/day	Duration	C_{max} (μg eq/g)		T_{max} (hr)		AUC_{0-t} (μg eq.•hr/g)	
			Fast	Slow	Fast	Slow	Fast	Slow
Plasma	7.5	Day 1						
		Week 6						
		Week 13						
	12.50	Day 1						
		Week 6						
		Week 13						
RBC	7.50	Day 1						
		Week 6						
		Week 13						
	12.50	Day 1						
		Week 6						
		Week 13						

The radioactive dose was excreted rapidly following oral dosing. Greater than 80% of the dose was excreted in the first 48 hours after dosing. The primary route of elimination of total radioactivity was fecal excretion. Approximately › of the dose was excreted via the feces suggesting extensive biliary and/or intestinal secretion of radioactivity. The total recovery of the radioactive dose in urine and feces combined ranged from at 168 hours postdose. No sex differences were noted in the excretion total radioactivity. Summary of the percent of radioactive dose excreted in urine and feces of dogs (Groups 6 and 7) following a single oral dose of SC-58635 on Day 1, and during Weeks 6 and 13 are presented in the below table.

Dose mg/kg/day	Dosing Interval	% Radioactive Dose					
		Urine		Feces		Total	
		♂	♀	♂	♀	♂	♀
7.50	Day 1	0.49	0.56	96.2	105	96.9	106
	Week 6	0.77	0.73	91.8	92.2	92.8	93.2
	Week 13	0.41	0.87	94.1	90.9	94.8	92.4
12.50	Day 1	0.64	1.25	93.9	92.5	95.1	94
	Week 6	0.43	1.06	90.8	96.4	91.3	97.9
	Week 13	0.37	1.35	92.2	90.3	93.3	92.3

There was no apparent induction of microsomal cytochrome P450 following the daily oral administration of SC-58635 for 13 weeks to male and female dogs. The mean microsomal

cytochrome P450 contents from males ranged from nmole/mg protein and were not dose-dependent. The mean microsomal cytochrome P450 contents in females ranged from protein and were also not dose-dependent. The following table shows total Cytochrome P450 Content, microsomes and total protein yield of dog liver, following oral administration of SC-58635 for 13 weeks.

Group	Dose mg/kg/day	P450 (nmole/mg protein)		Microsome Yield (mg/g liver)		Total Protein Yield	
		Male	Female	Male	Female	Male	Female
1[a]	Control	0.641 ± 0.0526[b]					
2	15						
3	25						
4	35						
5	25						

3.5.1.2. Evaluation Of Total Radioactivity Data For A 52-Week Capsule Toxicity Study With SC-58635 In Dogs, SA4425, Document No.: M2096056; Date: 09-Apr-1997 (Vol. 1.75, p. 131-254)

Study Nº: CHV 700-338/SA4425
Report Nº: M2096056
Study Aim: (1) To identify toxic effects of SC-58635 when administered orally to dogs for at least 26 or 52 weeks and (2) to assess the reversibility of any toxic effects of the test compound following a 4-week recovery period; (3) To determine the relationship of plasma concentration of test material to the duration of dosing; and (4) To evaluate evidence for sex-related differences in PK parameters.
Compound: SC-58635 (Lot Nº 94K014-A2B), SC-58635 (Lot Nº GDS 4671-90, 2.08 μCi/mg)
Vehicle: Empty gelatin capsule
Dosage: 0, 15, 25, and 35 mg/kg/day po for 52 weeks
Animals: 56 & 56 beagle dogs, ~7 months old, weighing kg for the ♂ and for the ♀.

Main and Recovery Study				Satellite PK Study			
Group	Dose (mg/kg/dose)	Dose (mg/kg/day)	Nº of Animals/Sex	Group	Dose (mg/kg/dose)	Dose (mg/kg/day)	Nº of Animals/Sex
1	0	0	12	6	7.5	15	4
2	7.5	15	8	7	17.5	35	4
3	12.5	25	8	4/sex from Groups 1-5 were sacrificed at Week 26.			
4	17.5	35	12	Dogs in Groups 1-4 & 6-7 received SC-58635 2x/day.			
5	25.0	25	8	Dogs in Groups 6 & 7 received SC-58635 as 1st daily dose on Day1 and Weeks 26 and 52.			

Study Location:

Compliance with GLP/QAU: Yes
Experimental Design: Dogs were given SC-58635, 0, 7.5x2, 12.5x2, 17.5x2 or 25x1 mg/kg/day in gelatin capsule orally gavage for at least 52 weeks; dosing continued through the day before terminal sacrifice (Weeks 52). Recovery animals were kept without treatment for an additional 4 weeks. Dogs in the companion PK study group received SC-58635 on Days 1, 176 & 358 and received nonradiolabeled SC-58635 on other days during the study. Blood samples were collected at 0.5, 1, 2, 3, 4, 5, 7, 12, 13, 14, 15, 18, 24 and 96 hr following the ingestion of radiolabeled

[ ]SC-58635. Urine and fecal samples were collected for 168 hr after each radiolabeled dose approximate 24-hr intervals.

Results: In the current report, information on plasma and RBC radioactivity concentrations and excretion data following [ ]SC-58635 administration to Groups 6 and 7 dogs on Days 1, 176 and 358 was included.

- Plasma and RBC Radioactivity - The concentrations of radioactivity in the cellular fraction of blood were higher than in plasma. Plasma T_{max} on Day 1 was 2 to 4 hours postdose in both males and females. Plasma T_{max} on Days 176 and 358 was 14 hours postdose in ♂ and 2 to 4 hours postdose in ♀. The time versus concentration profiles show an initial absorption and elimination phase followed by a second increase in concentrations of radioactivity subsequent to the p.m. dose of nonradiolabeled SC-58635. In males, this second increase in plasma concentration was higher than the initial increase on Days 176 and 358, accounting for the delayed C_{max} values in males. The plasma C_{max} values for radioactivity were higher in ♂ than ♀ on Days 1 and 176 but not Day 358. The plasma C_{max} values increased with increasing dose.
  RBC T_{max} on Day 1 occurred from 2 to 4 hours postdose in both ♂ and ♀. On Days 176 and 358 it occurred from 13 to 14 hours postdose in ♂ and from 2 to 4 hours postdose in ♀. The red blood cell C_{max} values for radioactivity were higher in ♂ than ♀ on Days I and 176. The red blood cell C_{max} values increased with increasing dose.
  A comparison of plasma and red blood cell concentrations from animals identified phenotypically as slow or fast metabolizers of [ ]SC-58635 showed concentrations in slow metabolizing animals to be higher than fast metabolizers.

Sampling Time (hr)	Concentration of Radioactivity (μg equivalents/g)							
	PLASMA				RED BLOOD CELLS			
	7.5 mg/kg/dose		17.5 mg/kg/dose		7.5 mg/kg/dose		17.5 mg/kg/dose	
	♂	♀	♂	♀	♂	♀	♂	♀
	Day 1							
0.5								
1								
2								
4								
7								
12								
13								
14								
15								
18								
24								
48								
96								
	Day 176							
0.5								
1								
2								
4								
7								
12								
13								
14								
15								
18								
24								
48								
96								
	Day 358							
0.5								
1								
2								
4								
7								
12								
13								
14								
15								
18								
24								
48								
96								

ND = Not Detectable (≤2x background)

APPEARS THIS WAY
ON ORIGINAL

Concentration of Radioactivity								
Sampling	Plasma				Red Blood Cells			
Time	Slow Metabolizer		Fast Metabolizer		Slow Metabolizer		Fast Metabolizer	
(hr)	7.5 mg/kg	17.5 mg/kg	7.5 mg/kg	17.5 mg/kg	7.5 mg/kg	17.5 mg/kg	7.5 mg/kg	17.5 mg/kg
	Day 1							
0.5								
1								
2								
4								
7								
12								
13								
14								
15								
18								
24								
48								
96								
	Day 176							
0.5								
1								
2								
4								
7								
12								
13								
14								
15								
18								
24								
48								
96								
	Day 358							
0.5								
1								
2								
4								
7								
12								
13								
14								
15								
18								
24								
48								
96								

ND = Not Detectable (≤2x background).

- Excretion - The major route of excretion of radioactivity was via the feces. The percent of dosed radioactivity excreted in the feces ranged from over the 168-hour collection period with urinary excretion accounting for There were no apparent effects of dose, duration of dosing, or sex in the patterns of excretion on different days or at different dose levels. The mean total recoveries ranged from for males and females at all dose levels on all dose days.

- Percent of radioactive dose in urine, feces, pan rinse, cage wash, cage wipe, and urine wipe at specified intervals postdose for ♂ and ♀ dogs following a single oral dose of SC-58635, 7.5 or 17.5 mg/kg, on Days 1, 176 and 358 are presented in the following table.

% Radioactive Dose										
Dose	Collection	♂	♀	♂	♀	♂	♀	Collection	♀	♂
mg/kg	Time (hr)	Urine		Feces		Pan Rinse		Time (hr)	Cage Wash, Cage/Urine Wipe	
Day 1										
7.5	0-24									
	24-48									
	48-72									
	72-96									
	96-120									
	120-144									
	144-168									
	Subtotal									
17.5	0-24									
	24-48									
	48-72									
	72-96									
	96-120									
	120-144									
	144-168									
	Subtotal									
Day 176										
7.5	0-24									
	24-48									
	48-72									
	72-96									
	96-120									
	120-144									
	144-168									
	Subtotal									
17.5	0-24									
	24-48									
	48-72									
	72-96									
	96-120									
	120-144									
	144-168									
	Subtotal									
Day 358										
7.5	0-24									
	24-48									
	48-72									
	72-96									
	96-120									
	120-144									
	144-168									
	Subtotal									
17.5	0-24									
	24-48									
	48-72									
	72-96									
	96-120									
	120-144									
	144-168									
	Subtotal									

ND = Not detectable; < 2x background; [a] Cage wash (MeOH); [b] Cage wash (TSP); [c] Cage wipe; [d] Urine wipe; [e]Includes urine, feces, pan rinse, cage wash, cage wipe, and urine wipe.

3.6. Bioanalytical Procedures

The following study reports related to analytical method development and validation were submitted to the present NDA but were not reviewed.

APPEARS THIS WAY
ON ORIGINAL

4. LABELING REVIEW:

5. SUMMARY AND EVALUATION:

5.1. PHARMACOLOGY/PHARMACODYNAMICS

5.1.1. ACTION-RELATED PHARMACOLOGY

SC-58635 was demonstrated to have following properties.

5.1.1.1. *In Vitro* -

SC-58635 preferentially inhibited COX-2 mediated PGE_2 production by human whole blood and dog whole blood.

5.1.1.2. *In Vivo* -

- Anti-inflammatory Activity - SC58635 was effective in the following animal models.
  (1) carrageenan-induced rat paw edema model with an ED_{50} value of 7 ± 1 mg/kg;
  (2) adjuvant induced arthritis in rats by the inhibition of cartilage destruction, bone lysis, bone proliferation, soft tissues edema and synovial iflammation with an ED_{50} value of 0.3 ± 0.1 mg/kg; and
  (3) carrageenan-induced air pouch in rats by the inhibition of PGE_2 and 6-keto $PGE_{1\alpha}$ with an ED_{50} value of 0.2 ± 0.1 mg/kg.
- Analgesic Activity - SC58635 was effective in the following animal models.
  (1) Hargreaves' hyperalgesia model with an ED_{50} value of 0.35 mg/kg;
  (2) formalin induced hyperalgesia in the mose hindpaw modei;
  (3) pheyl-benzoquinone induced doxoflexion in mice; and
  (4) acetic acid-induced writhing in mice.
- Anti-pyretic Activity - SC58635 was shown to reduce LPS-induced fever but did not alter normal temperature in rats.
- Chemoprevention Properties - Reports indicated that administration of SC58635 in the diet to rats at inhibit azoxymethan-induced colonic aberrant cryptic foci and tumors. Reports show that NSAIDs use in the general population is associated with a reduced risk of colon cancer death[14]. It has been demonstrated that colorectal tumors have elevated levels of COX-2[15,16]. The mechanism of chemoprevention by NSAIDs is not clear. However, NSAIDs induced apoptosis in human colorectal cancer cells has been demonstrated[17].

14 Thun, MJ, 1995. Gastroenterol Clin North Am. 25: 333-348.
15 Tsujii, M. and Bubois, RN, 1995. Cell 83: 493-501
16 Morin, PJ, Vogelstein, B and Kinzler, KW, 1996. Proc. Natl. Acad. Sci. USA 93: 7950-4820.
17 Chan, TA, et al., 1998. Proc. Natl. Acad. Sci. USA 95: 681-686.

5.1.2. *SAFETY PHARMACOLOGY*

A summary of safety pharmacology study reports is presented in the following table.

Study Type	Species	Dose/Route	Results
Effect on General Activity and Behavior			
General Activity and Behavior	Mice, 3/group	0, 50, 150, or 500 mg/kg po	50 & 150 mg/kg: slightly ↓ locomotive activities. 500 mg/kg: ↑ in locomotive activities in ⅓ mice.
Effect on Central Nervous System			
Spontaneous Locomotor Activity	Mice, 10/group	0, 50, 150, or 500 mg/kg po	500 mg/kg: significantly ↓ spontaneous locomotive activities by 87% as compared to control animals at 3 hr post dosing.
Effect on Hexobarbital-Induced Sleep			↑ hexobarbital-induced sleep dose-dependently
Electroshock-Induced Convulsions	Synergestic		≥150 mg/kg: slightly ↓ the incidences of clonic convulsions, the incidences of tonic and mortality were not affected.
	Antagonistic		↓ incidences of tonic convulsions dose-dependently, the incidences of clonic and mortality were not affected.
Chemical-Induced Convulsions	Synergestic		≥150 mg/kg: significantly ↓ the incidences of clonic convulsions, the incidences of tonic and mortality were not affected.
	Antagonistic		dose-dependently ↓ the incidences of tonic convulsions and mortality, the incidences of clonic were not affected.
Analgesic Activity			Significantly ↓ acetic acid-induced writhing in dose-dependent fashion, but had no effect on tail pinch-induced pain.
Body Temperature	Rat, 8/group	0, 50, 150, or 500 mg/kg po	↔ (no effect)
Effect on Autonomic Nervous System and Smooth Muscle			
Spontaneous Motility	Guinea Pig Isolated Ileum		≥$4x10^{-6}$: significantly ↓ the amplitude of spontaneous motility
Agonist-induced Contraction			≥$4x10^{-7}$ M: ↓ $BaCl_2$-induced contractions; ≥$4x10^{-6}$ M: ↓5-HT-induced contractions; ≥$4x10^{-5}$ M: ↓ ACh-, Histamine-induced contractions.
Effect on Digestive system	Mice, 10/group	0, 50, 150, or 500 mg/kg po	↔ on the rate passage of charcoal meal in small intestine.
Effect on Respiratory and Cardiovascular Systems	Dog, 3/group	0, 50, 100 or 200 mg/kg	200 mg/kg: ↑ blood flow significantly, ↔ on the ECG, and PR, QT, and QRS interval times, systolic, diastolic, and mean blood pressure, heart rate and respiratory pressure
Effect on Urine Volume, Urinary PGE_2, and Urinary Electrolytes Excretion	Rat, 8/group	0, 50, 150, or 500 mg/kg po	↓ urine volume significantly up to 6 hr postdose, and Na^+, Cl^- excretion; ↑ urinary osmolarity significantly; ↔ on K^+ excretion and pH.
		0, 5, 15, 50, mg/kg po	50 mg/kg: similar effects were obtained as previous test. 15 mg/kg: ↓ urine volume at 3 hr postdose; ↑ urinary osmolarity for 6 hr, excretion of urine electrolytes were not affected.
	♂ Rat, 6/group	600 mg/kg/day x7	↔ urine volume, urinary PGE_2 ↓ kidney PGE_2
	♀ Rat, 8/group	600 mg/kg/day x3 or x7	↔ urine volume, urinary PGE_2

5.2. TOXICOLOGY

APPEARS THIS WAY ON ORIGINAL

5.2.1. *ACUTE (SINGLE-DOSE)*

Single-dose oral toxicity of celecoxib was accessed in the rat, dog and cynomolgus monkey. Results are listed in the following table.

Species Nº of Animal/Group	Dose (mg/kg)/Route	Length of Observation	Observations	NOAEL (mg/kg)
SPF Crj:CD(SD) Rats 5/sex/group	0, 1000, or 2000 po by gavage	2-Week	White stool was seen in ♂ & ♀ @ 2000 mg/kg on the day of dosing.	2000
♂ Beagle Dogs 2/group	1000 and 2000 po	2-Week	Vomiting and test article like substance in the stool were noted.	2000
♀ Cynomolgus Monkeys 3/group	25 and 250 po	2-Week	Watery stool was seen on Day 1 in one animal from each treatment group. The one receiving 25 mg/kg/day also showed blood in the stool on Day 2 but not on Days 3-14.	25

5.2.2. *REPEATED-DOSE*

The repeated-dose toxicity of SC-58635 was evaluated in mice, rats, and dogs. Findings from each study are summarized as followings.

Species N° of Animal	Dose (mg/kg)	Duration and Route	Findings	NOAEL (mg/kg)
CD-1 Mice 10/sex/group	0, 100, 300, 1000 & 3000 qd	2-Wk Diet Admix	≥1000: Deaths occurred with clinical signs of hunched posture, shivering, reduced activity and reduced fecal output; ↓ in body weights and food consumption; a slight ↑ in liver/body weight ratios; GI (perforated ulcers with secondary peritonitis) and kidney (renal tubule degeneration/regeneration) were the major target organs.	♂: 100 ♀: 300
CD-1 Mice 20/sex/group	♂: 0, 75, 150, 300 qd ♀: 0, 150, 300, & 1000 qd	13-Wk Diet Admix	Deaths (1♂ @ 75 mg/kg, one ♂ @ 150 mg/kg, 5♂ & 1♀ @ 300 mg/kg and 15♀ @ 1000 mg/kg) observed as a result of SC-58635 treatment related GI toxicity and secondary peritonitis; a significant ↓ in food consumption , in ♀ @ 1000 mg/kg; a dose-dependent ↓ in serum triglycerides (♂ & ♀ @ ≥150 mg/kg); GI (perforated ulcers with secondary peritonitis) was the major target organ. Inconclusive nephropathy was noted.	♂: Not Determin-able ♀:150
Crl:CD®(SD)BR Rats 5/sex/group	100→ 200 →400→600 →800 qd	15-Day Dose Escalation (3-Day/Dose) Oral Gavage	mild→moderate liver enlargement; ↑ cytochrome P-450 content per mg protein (1.8x); slight mild hypertrophy of centrilobular hepatocytes.	
Crl:CD®(SD)BR VAF/Plus® Rats 10-15/sex/group	20, 40, 80, 400, & 600 qd	4-Wk with 4-Wk Recovery Oral Gavage	Deaths (1♀ @ 600 and 1♂ @ 400) occurred as a result of SC-58635 treatment related toxicity (perforation of Jejunum with peritonitis in ♀ and pyelonephritisin ♂); statistically significant ↑ absolute liver weights and liver/body weight ratios without corresponding microscopic findings were identified for ♀ @ 400 or 600 mg/kg.	♂: 80 ♀: 400
Crl:CD®(SD)BR Rats 25/sex/group	0, 20, 80, & 400 qd	13-Wk with 4-Wk Recovery Oral Gavage	Marked elevations in ALT (524 and 574 U/l, respectively), AST (640 and 815 U/l, respectively), and sorbitol dehydrogenase (SDH) (134 and 136, respectively) at Week 18 in 1♂ each at 20 and 80 mg/kg and ↑ALT, AST, and SDH (~2-3x relative to control values) in ♂ at Weeks 6 and/or 14 (1 @ 20, 2 @ 80 and 3 @ 400 mg/kg) without corresponding histopathological alterations were identified. Minimal→slight changes in the liver with centrilobular to midzonal hepatocellular enlargement was seen in both high dose ♂ and ♀ rats. Minimal or slight degeneration of the renal papilla was noted in 1♂ @ 80 mg/kg/day and 3♂ @ 400 mg/kg/day but not in ♀ or rats in recovery phase. There were no treatment-related microscopic changes in the GI tract.	♂: 400 ♀: 400
Crl:CD®(SD)BR Rats 25/sex/group	0, 20, 80, & 400 qd	26-Wk with 4-Wk Recovery Oral Gavage	Deaths (1♀ @ 80 and 6♀ @ 400) occurred as a result of SC-58635 treatment related GI injury (necrosis in jejunum with moderate→severe peritonitis).	♂: 400 ♀: 20
♂ & ♀Beagle Dogs 3/group	0, 15, 40 qd	7-Day iv	High levels of PGE_2 were present in the stomach and colon. SC-58635 caused ↓ in blood TBX and PGE_2 levels. GI lesions (pyloric-duodenal ulcer/erosion) in one dog @ 40 mg/kg after repeated iv dosing for 7 days.	15
Beagle Dogs 4-8/sex/group	0, 20, 25, 50, 100, & 250 qd	4-Wk with 4-Wk Recovery Oral	Treatment caused deaths (ulceration of pylorus, jejunum, duodenum, and ileum) were seen in dogs @ ≥50 mg/kg day. Low incidence of interdigital pyoderma and subcutis abscess was noted in dogs at @ ≥50 mg/kg/day. Inconclusive histopathological changes in the brain (mild→moderate periventricular/perivascular lymphocytic infiltration) were noted.	25
Beagle Dogs 4-8/sex/group	0, 7.5, 12.5, 17.5 bid & 25 qd	13-Wk with 4-Wk Recovery Oral	No remarkable findings were attributable to the treatment.	17.5 bid
Beagle Dogs 4-8/sex/group	0, 7.5, 12.5, 17.5 bid & 25 qd	52-Wk with 4-Wk Recovery Oral	Not remarkable.	17.5 bid

5.2.3. *CARCINOGENICITY*

The carcinogenic potentials of SC-58635 were accessed in rats and mice.

Rat Study - Groups of rats were given SC-58635 in 0.5% methylcellulose (w/v) + 0.1% polysorbate 80 as a suspension once daily by oral gavage at a dose schedule as shown in the following table for 104 weeks.

Group	Dose mg/kg/day				
	Wk 1-17	Wk 18-77		Wk 78-104	
	♂ & ♀	♂	♀	♂	♀
1 (Control)	0	0	0	0	0
2 (Low)	20	20	20	20	5
3 (Mid)	80	80	80	80	10
4 (High)	400	400	200	200	200

The doses selected in this study were based on the results of a 4-week oral gavage study at doses of 0, 20, 80, 400 and 600 mg/kg in which it was shown that absorption of SC-58635 attained a plateau at dosages ≥400 mg/kg/day for ♂ rats and deaths were seen at 600 mg/kg/day for ♀ rats. Based on GI (necrosis/perforation/inflammation with secondary peritonitis) and kidney (pyelonephritis, ♂ only) toxicity findings as well as mortality observed in this study, MTD was reached for both ♂ and ♀. There was no treatment-induced increases in the tumor incidence rates. The exposure to SC-58635 in the high dose ♀ rats, as measure by AUC_{0-24} was ~20 and 10x of that observed in humans at the doses of 200 and 400 mg/day, respectively. The exposure of the high dose ♂ rats to SC-58635, was ~10 and 5x of that observed in humans at 200 and 400 mg/day, respectively. The NOAEL for ♂ was 20 mg/kg and was not perceptible for ♀.

Mouse Study - Groups of mice were given celecoxib at the doses shown in the following table via dietary admix.

Group	Dose (mg/kg)				
	♂		♀		
	Wk1-18	Wk 19-104	Wk1-18	Wk19-22	Wk 23-104
N	0*	0	0	0	0
1	25	12.5	50	25	25
2	50	25	100	50	50
3	75	37.5	150	75	150

The doses selected in this study were based on toxicity findings of a 13-week dietary admix (♂: 0, 75, 150 and 300 mg/kg; ♀: 0, 150, 300 and 1000 mg/kg). Due to excessive toxicity, high dose group (♂ and ♀) was terminated at Week 80. Treatment-caused histopathological changes were limited to the GI tract (erosion/ulceration with associated chronic active inflammation in the glandular stomach, duodenum, jejunum, ileum, cecum, and colon at one or more sites). Low incidence of pyelonephritis was noted in the ♂ mice. The GI injury was the most common cause of death in high-dose animals. Therefore, the MTD was reached. No treatment-induced increases in the tumor incidence rates were identified. The exposure to SC-58635 in the high dose ♂ and ♀ mince was equivalent to ~2-3x of values seen in humans (200 or 400 mg/day). The NOAEL for either ♂ or ♀ could not be determined for this study as treatment-induced toxicity was observed in all SC-58635 treated groups.

5.2.4. *REPRODUCTIVE TOXICOLOGY*

The following table summarizes the effects of SC-58635 on fertility, reproductive functions, embryo-fetal development, and peri-/post-natal development.

Animals Species	Dose (mg/kg)	Duration of Treatment	Observations	NOAEL (mg/kg)
FERTILITY, EARLY EMBRYONIC DEVELOPMENT→IMPLANTATION				
♂ & ♀ Rats Crl:CD®(SD)BR	0, 60, 300, 600	♂: ≥28 days prior to mating → the end of study ♀: 14 day prior to mating→Gestation Day 7	≥ 60 mg/kg: ↓ live fetuses and implantation sites; ↑ preimplantation loss.	♂: 600 ♀: <60
♀ Rats Crl:CD®(SD)BR	0, 15, 30, 50, 300	14-day prior to mating→Gestation Day 7	≥50 mg/kg: ↓ live fetuses and implantation sites; ↑ pre- and post-implantation loss. 300 mg/kg: ↓ corpora lutea	30
♀ Rats Crl:CD®(SD)BR	0, 60, 300	14-day followed by a 14-day reversal period before mating	No effects.	300
TERATOLOGY- EMBRYO-FETAL DEVELOPMENT				
♀ CD Rats VAF	0, 10, 30, 100	Gestation Days 6→17	100 mg/kg: slight ↓ live fetuses. ≥30 mg/kg: ↑ incidence of wavy ribs	30
♀ Rats Crl:CD®(SD)BR	0, 10, 30, 100	Gestation Days 6→17	≥30 mg/kg: ↑ incidence of diaphragmatic hernia, 5th sternebrae incomplete ossification	10
♀ Rabbits Hra: (NZW)SPF	0, 6, 30, 60, 300, 600	Gestation Days 7→18	600 mg/kg: ↓ body weights and food intake; ↑post-implantation loss; ↓ live fetuses.	300
♀ Rabbits Hra: (NZW)SPF	200, 400, 600	Gestation Days 19/21→23/25	600 mg/kg: ↓ body weights (5%)	600 (?)
♀ Rabbits Hra: (NZW)SPF	0, 60, 150, 300	Gestation Days 7→18	≥150 mg/kg: slight ↑ sternebrae fused and sternebrae misshapen 300 mg/kg: slight ↑ rib fused; ↑ post-implantation loss; ↓ live fetuses.	60
PERINATAL/POST NATAL DEVELOPMENT				
♀ Rats Crl:CD®(SD)BR	0, 10, 30, 100	Gestation Day 6→Days 21-23 post partum	F_0 - ≥30 mg/kg: Deaths or Moribund (1 @ 30, 8 @ 100 mg/kg) with GI lesions; transient ↓ in food consumption (Gestation Days 6-9); ↓ live pups; ↑ dead pups. F_1 & F_2 - Normal.	10

A comparison of exposure to SC-56835 on the last day of dosing in rat and rabbit reproductive study to human clinical exposure is presented in the following table.

Species	NOEL (mg/kg)	Exposure in Animal		Ratio of Animal Exposure/Human Exposure to SC-58635			
				200 mg/day[a]		400 mg/day[a]	
		C_{max} (μg/ml)	AUC_{0-24} (μg•hr/ml)	C_{max}	AUC_{0-24hr}	C_{max}	AUC_{0-24}
Embryo-Fetal Developmental							
Rat	10						
Rabbit	60						
Pre-Mating and Early Pregnancy							
Rat	30						

[a] The mean C_{max} and AUC_{0-24} values for the 200 mg/day dose were 0.675 μg/ml and 8.40 μg•hr/ml, respectively and the mean C_{max} and AUC_{0-24} values for the 400 mg/day dose were 1.35 μg/ml and 16.8 μg•hr/ml, respectively. Ratio was calculated by dividing animal Day last AUC_{0-24hr} or C_{max} values by respective human values.

APPEARS THIS WAY ON ORIGINAL

5.2.5. *GENETIC TOXICOLOGY*

The mutagenic potentials of celecoxib were evaluated in both *in vitro* and *in vivo* systems and results are summarized in the following table.

Assay System	Indicator Cells	SC-58635 Conc.	Findings
Ames	*Salmonella typhimurim* strains (histidine auxotrophs) TA97a, TA98, TA100, TA1535 and TA1538	10, 50, 100, 500, 1000, and 5000 μg/plate	Toxic at concentrations of ≥500 μg/plate Not mutagenic at concentrations up to 500 μg/plate
CHO/HGRT Mutation	CHO cells (subline K1-BH4)	Range-Finding: -S9: 4, 8, 12, and 16 μg/ml +S9: 15, 30, 45, and 60 μg/ml	Not mutagenic at doses up to 16 μg/ml and 45 μg/ml in the absence and presence of S9 activation, respectively.
Chromosome Aberration	CHO-WBL cells	Range-Finding: -/+ S9: 10, 20, and 40 μg/ml	+S9: ↑ frequency in cell endoreduplication. Slight but not significant ↑ in % cells with aberration.
Micronucleus Assay	♂ & ♀ Crl:CD®(SD)BR Rats - Bone Marrow Cells	150, 300, and 600 mg/kg/day po for 3 days	Not clastogenic

5.2.6. *SPECIAL TOXICOLOGY*

The antigenic properties and the potentials to cause skin sensitivity, dermal or ocular irritations of celecoxib were evaluated and the observations are summarized in the following table.

Testing System	Species	SC-58635 (Dose/Route)	Observations/Comments
ANTIGENIC PROPERTY			
ASA, HmPCA (4 hr), and HtPCA Rxns[a]	♂ Guinea Pigs	Sensitization: 5, 25 po or 25 mg/kg sc Challenge: 5 mg/kg iv	Not antigenic.
SKIN CONTACT SENSITIVITY/DERMAL/OCULAR IRRITATION			
Guinea Pig Maximization Test	Crl:(HA)BR Albino Guinea Pigs	Sensitization: 5% in FCA/H_2O id[b] Induction and Challenge 25% in Petrolatum dermal topical	**No concurrent + control was performed. Therefore, the study was not valid.**
Primary Skin Irritation	♂ Hra:(NZW)SPF Rabbits	0.5 g dermal occlusion	No dermal irritation.
Primary Eye Irritation	♂ Hra:(NZW)SPF Rabbits	0.011 g (0.1 ml wt equivalent) lower everted eye lid	Minimal ocular irritation.

[a] ASA = Active Systemic Anaphylaxis; HmPCA = Homologous Passive Cutaneous Anaphylaxis; HtPCA = Heterologous Passive Cutaneous Anaphylaxis; Rxns = Reactions.

[b] FCA = Freund's Complete Adjuvant; id = intradermal injection

5.2.7. *Toxicity Related To The Stating Material (SC-70986, 4-Sulfonamidophenyl Hydrazine Hydrochloride) For Synthesis of SC-58635*

The following table shows the summary of toxicological findings for the stating material (SC-70986, 4-sulfonamidophenyl hydrazine hydrochloride) in various studies.

Testing System	Species/Indicator	SC-70986 Dose/Route	Findings
Acute Toxicity	♂ & ♀ Rats Crl:CD®(SD)BR	250, 500, 1000, and 2000 mg/kg/ ml po	LD_{50}: ♂, 1000 (558-1792); ♀, 707 (483-1036). Clinical Signs: Hyporeactivity, staggered gait, absence of gasping/righting reflex, prostration, clonic convulsions, thin appearance, hunched posture, red-stained face, excessive salivation, lacrimation, mydriasis, dyspnea, soft stool, wet and/or yellow-stained urogenital area
Primary Eye Irritation	Rabbits Hra:(NZW) SPF	73 mg lower eyelid	Unflashed: corneal and iridal involvement and moderate conjunctival irritation. Flushed: corneal involvement and slight conjunctival irritation.
Primary Dermal Irritation	Rabbits Hra:(NZW) SPF	0.5 g in 0.4 ml dist. H_2O applied to skin directly	Slight skin irritant.
Dermal Sensitivity (Guinea Pig Maximization Test)	guinea pigs Crl:(HA)BR	Sensitization: 5% in H_2O or FCA/H_2O id[b] Induction and Challenge: 25% in Petrolatum, dermal topical	**Extreme dermal sensitizer**: mild→intense skin reactions were noted in all animals in the test group; Some animals (12/20) in the test group showed subcutaneous hemorrhaging, necrosis, and desquamation in the test sites following challenge.
Salmonella/microsomal Ames Assay	*Salmonella typhimurium*: histidine auxotrophs TA97a, TA98, TA100, TA102, and TA1535	10-5000 μg/plate	**Mutagenic**: ≥50 μg/plate, -S9 - TA97a and TA102 ≥100 μg/plate, + S9 - TA97a 5000 μg/plate, +/- S9 - TA98 and TA100

5.3. ADME

5.3.1. *Absorption (Bioavailability) and Toxicokinetics*

APPEARS THIS WAY ON ORIGINAL

5.3.1.1. Single IV Studies

Assessment of the intravenous (iv) pharmacokinetics of celecoxib was conducted in five species. The following table presents the summary of mean plasma PK parameters (SEM) following single dose iv administration of SC-58635.

Species	Dose (mg/kg)	$t_{1/2}$ (hr)		Vd_{ss} (l/kg)		Vd_{β} (l/kg)		Cl (ml/min/kg)		$AUC_{0-\infty}$ (μg•hr/ml)	
		♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Rat (N=3)	1	3.73	14.0	2.51	2.42	ND	ND	7.76	1.99	2.15	8.38
Rat (N=3)	10	3.49		1.86		ND	ND	5.81		28.7	
Guinea Pig (N=2)	6	1.16		1.98		ND	ND	20.5		5.49	
Dog (N=3)	1	3.92 (1.41)	4.09 (1.92)	2.30 (0.32)	2.30 (0.59)	ND	ND	10.0 (2.9)	7.98 (2.00)	2.00 (0.49)	2.52 (.52)
Dog (N=2)	5	8.84		2.42		ND	ND	3.08		31.2	
Dog (Fast) (N=3)	5	1.77 (0.25)	1.66 (0.16)	2.63 (0.43)	2.32 (0.15)	2.18 (0.20)	1.98 (0.05)	19.2 (2.2)	16.9 (1.6)	4.95 (0.47)	5.20 (0.47)
Dog (Slow) (N=3)	5	4.69 (0.44)	5.54 (0.36)	2.95 (0.21)	3.27 (0.21)	2.26 (0.09)	2.45 (0.09)	7.43 (0.44)	6.95 (0.45)	11.5 (0.7)	12.5 (0.7)
Cynomolgus Monkey (N=3)	1		1.66 (0.50)		3.58 (1.02)		3.22 (0.88)		22.7 (1.0)		0.736 (0.032)
Rhesus Monkey (N=3)	1		1.50 0.10)		2.73 (0.34)		2.34 (0.41)		17.8 (1.9)		0.957 (0.096)

ND = Not determined.
Fast = Dogs of the phenotype that eliminate SC-58635 from plasma at a fast rate
Slow = Dogs of the phenotype that eliminate SC-58635 from plasma at a slow rate.

5.3.1.2. Single Oral Studies

A summary of mean (SEM) plasma PK parameters for SC-58635 following single dose oral administration is shown in the following table.

Species (N)	Dose (mg/kg)	Sex	T_{max} (hr)	C_{max} (μg/ml)	$AUC_{0-\infty}$ (μg•hr/ml)	BA %
Rat (3)	2	♂	3.00	0.599	ND	ND
Rat (3)	10	♂	3.00	2.01	18.5	64.5
Dog (3)	1	♂	1.00 (0.50)	0.309 (0.015)	1.57 (0.32)	74.4 (5.6)
Dog (3)	1	♀	0.667 (0.167)	0.553 (0.070)	2.12 (0.47)	85.9 (20.7)
Dog (2)	5	♀	0.500	2.19	16.2	57.1
Dog (2)	5	♀	3.00	0.517	4.80	16.9
Dog-Fast (3)	5	♂ & ♀	0.667 (0.167)	0.822 (0.219)	2.63 (0.59)	63.7 (10.5)
Dog-Slow (3)	5	♂ & ♀	0.500 (0)	1.54 (0.19)	10.5 (1.6)	88.0 (5.8)

ND = Not determined; N = The number of animals.
Fast = Dogs of the phenotype that eliminate SC-58635 from plasma at a fast rate.
Slow = Dogs of the phenotype that eliminate SC-58635 from plasma at a slow rate.

The following table presents the food effect on mean SC-58635 PK (±SEM) parameters in beagle dogs.

Site of Absorption and Food Effect Studies in Beagle Dogs								
Dose (mg/kg)	Route	Diet	T_{max} (hr)		C_{max} (μg/ml)		AUC_{0-24} (μg•hr/ml)	
			♂	♀	♂	♀	♂	♀
10 n=4	IG[a]	Fasted		0.688 ± 0.277		1.62 ± 0.36		10.3 ± 2.0
	Duodenum[a]			1.13 ± 0.63		1.46 ± 0.20		9.69 ± 1.57
	Jejunum[a]			2.25 ± 1.92		1.06 ± 0.21		9.37 ± 0.97
	Colon[a]			8.50 ± 2.02		0.789 ± 0.118		10.0 ± 0.9
5 n=3/sex	IG[b]	Fasted	1.50 ± 0.29	7.50 ± 5.27	0.356 ± 0.163	0.364 ± 0.035	1.89 ± 1.01	3.32 ± 0.28
		Low Fat	3.00 ± 0.50	3.67 ± 1.17	0.712 ± 0.227	0.775 ± 0.064	5.63 ± 1.94	5.58 ± 1.09
		Med. Fat	5.33 ± 0.67	4.67 ± 0.67	0.706 ± 0.148	0.631 ± 0.080	5.07 ± 1.35	5.07 ± 0.83
		High Fat	6.00 ± 1.15	5.33 ± 1.76	0.737 ± 0.115	0.808 ± 1.06	6.64 ± 1.73	6.66 ± 1.34

[a]SC-58635 was administered as a solution in PEG:H_2O, 2:1, (v/v) or in PEG:Saline, 2:1, (v/v).
[b]SC-58635 was administered as neat chemical in a gelatin capsule.
Med. Fat = Medium Fat ; IG = Intragastrically.

5.3.1.3. Repeated-Dose Oral Toxicity Studies

Mouse Studies

The following table summarizes PK parameters obtained from 2-, 13-, and 104-week oral toxicity studies.

2-Week Diet Admix Study in Mice, EX4325			
Dose (mg/kg)	C_{max} (μg/ml)		AUC_{0-21} (μg•hr/ml)	
	♂	♀	♂	♀
100				
300				
1000				

13-Week Diet Admix Range-Finding Study in Mice, EX4357												
Dose (mg/kg)		C_{max} (μg/ml)						$AUC_{0-\infty}$ (μg•hr/ml)					
♂	♀	♂			♀			♂			♀		
		Day 1	Day 45	Day 87	Day 1	Day 45	Day 87	Day 1	Day 45	Day 87	Day 1	Day 45	Day 87
75													
150													
300													

104-Week Diet Admix Carcinogenicity Study, SA4452								
Week (Days)	Dose (mg/ kg)					C_{max} (μg/ml)		AUC_{0-24} (μg•hr/ml)	
	Wk1-18	Wk 19-104	Wk1-18	Wk19-22	Wk 23-80				
	♂		♀			♂	♀	♂	♀
1 (3- 4)									
19 (126- 127)									
52 (357- 358)									
78 (540- 541)									

Rat Studies

The following table summarizes PK parameters obtained from 4-, 13-, 26-, and 104-week oral toxicity studies.

4-Week Oral Toxicity Study (SA4261)								
Dose (mg/kg)	C_{max} (μg/ml)				AUC_{0-24} (μg•hr/ml)			
	Day 1		Day 26		Day 1		Day 26	
	♂	♀	♂	♀	♂	♀	♂	♀
20								
80								
400								
600								

13- and 26-Week Oral Toxicity Studies (SA4346 and SA4366*)								
Dose (mg/kg)	C_{max} (μg/ml)				AUC_{0-24} (μg•hr/ml)			
	Day 1	Day 42	Day 91	Day 182*	Day 1	Day 42	Day 91	Day 182*
20								
80								
400								

104-Week Carcinogenicity Study (SA4367)									
Group	Dose mg/kg/day	PK Parameter	Day 1 (Wk1)		Day 180 (Wk 26)		Day 359 (Wk 52)		Day 541 (Wk 78)	
			♂	♀	♂	♀	♂	♀	♂	♀
Low	20	C_{max} (μg/ml)								
	5									
Mid	80									
	10									
High	400									
	200									
Low	20	AUC_{0-24} (μg•hr/ml)								
	5									
Mid	80									
	10									
High	400									
	200									

The following table summarizes PK parameters obtained from reproductive toxicity studies.

Pre-Mating and Early Pregnancy Study in Rats				
Dose	C_{max} (μg/ml)		AUC_{0-24} (μg•hr/ml)	
(mg/kg)	Day 1[a]	Day 23[b]	Day 1	Day 23
5				
15				
30				
50				

[a] Animals were dosed 14 days prior to mating, throughout the mating period until day 7 of gestation. The total dosing period was approximately 23 days.
[b] Gestation Day 7

Embryo-Fetal Development Toxicity Studies in Rat (n=6/dose)				
Dose	C_{max} (μg/ml)		AUC_{0-24} (μg•hr/ml)	
(mg/kg)	Gestation Day 6	Gestation Day 16/17	Gestation Day 6	Gestation Day 16/17
SA4362 - Animals were dosed once daily from day 6 to day 16 of gestation.				
10				
30				
100				
SA4599 - Animals were dosed once daily from day 6 to day 17 of gestation.				
10				
30				
100				

Embryo-Fetal Development Toxicity Studies in Rabbit, SA4342 (n=6/dose)				
	Gestation Day 7	Gestation Day 19	Gestation Day 7	Gestation Day 19
60				
150				
300				

Dog Studies

Mean PK (±SEM) parameters for SC-58635 obtained from 4-, 13-, 26/52-week oral toxicity studies are summarized in the following tables.

4-Week Oral Safety Assessment Study in the Dog, SA4260							
Day of Dosing	Dose (mg/kg)[a]	C_{max} (μg/ml)			AUC_{0-24} (μg•hr/ml)		
		♂	♀	♂+♀	♂	♀	♂+♀
1	25 (n=4)	1.90 ± 0.79	1.72 ± 0.42	1.81 ± 0.42	21.7 ± 10.9	18.7 ± 6.7	20.2 ± 6.0
	50 (n=4)	4.15 ± 1.42	1.94 ± 0.66	3.04 ± 0.84	47.7 ± 13.3	25.4 ± 10.4	36.6 ± 8.9
	100 (n=8)	6.89 ± 1.54	3.96 ± 0.89	5.42 ± 0.94	104 ± 30	71.0 ± 19.9	87.3 ± 17.9
	250 (n=8)	10.3 ± 3.1	8.44 ± 2.05	9.37 ± 1.82	153 ± 53	120 ± 36	136 ± 31
15	100	8.35 ± 2.71	8.72 ± 3.34	8.51 ± 2.02	117 ± 41	104 ± 36	111 ± 27
	250	7.72 ± 2.98	12.0 ± 3.9	9.85 ± 2.43	135 ± 67	211 ± 80	173 ± 51
27	25	4.62 ± 2.58	2.27 ± 0.65	3.45 ± 1.31	71.5 ± 50.9	22.2 ± 7.8	46.9 ± 25.6
	50	6.77 ± 2.10	4.66 ± 2.04	5.86 ± 1.43	83.7 ± 30.2	60.6 ± 30.0	73.8 ± 20.3

[a] The 100 and 250 mg/kg dose groups were sacrificed on day 15 of dosing. The 25 and 50 mg/kg dose groups were sacrificed on day 27 of dosing. Reference: Document Number MRC-94S-0185.

13-Week Oral Safety Assessment Study in the Dog (SA4324)							
Dose (mg/kg)	Phenotype[b]	C_{max} (μg/ml)[a]			AUC_{0-24} (μg•hr/ml)		
		Day 1	Day 39	Day 88	Day 1	Day 39	Day 88
7.5 (bid)	Fast						
	Slow						
12.5 (bid)	Fast						
	Slow						
17.5 (bid)	Fast						
	Slow						
25 (qd)	Fast						
	Slow						

26/52-Week Oral Safety Assessment Study in the Dog (SA4324)							
Dose (mg/kg)	Phenotype	C_{max} (μg/ml)[b]			AUC_{0-24} (μg•hr/ml)		
		Day 1	Day 178	Day 360	Day 1	Day 178	Day 360
7.5 (bid)	Fast						
	Slow						
12.5 (bid)	Fast						
	Slow						
17.5 (bid)	Fast						
	Slow						
25 (qd)	Fast						
	Slow						

[a] The C_{max} value reported is the maximal plasma SC-58635 concentration obtained over a 24 hour dosing day.

[b] Phenotype: Fast are dogs of the phenotype that eliminate SC-58635 from plasma at a fast rate. Slow are dogs of the phenotype that eliminate SC-58635 from plasma at a slow rate.

The following table shows the comparison of exposures to SC-58635 on last day of dosing in rat and dog toxicity studies to clinical human exposures at 200 and 400 mg/day.

Species	Duration	Sex/ Pheno-type[b]	NOEL (mg/kg)	Animal Exposure (Last Day of Dosing)		Animal/Human Exposure Ratio[a]			
				C_{max} (μg/ml)	AUC_{0-24} (μg•hr/ml)	200 mg/day		400 mg/day	
						C_{max}	AUC_{0-24}	C_{max}	AUC_{0-24}
Rat	4-Wk	♂	80						
		♀	400						
Rat	13-Wk	♂	20						
		♀	20						
Rat	6-Mon	♂	20						
		♀	20						
Dog	4-Wk	♂	25						
		♀							
Dog	13-Wk	Fast (♂ & ♀)							
		Slow (♂ & ♀)							
Dog	6-Mon	Fast (♂ & ♀)							
		Slow (♂ & ♀)							
Dog	1-Year	Fast (♂ & ♀)							
		Slow (♂ & ♀)							

[a] The mean C_{max} and AUC_{0-24} values for the 200 mg/day dose were 0.675 μg/ml and 8.40 μg•hr/ml, respectively. The mean C_{max} and AUC_{0-24hr} values for the 400 mg/day dose were 1.35 μg/ml and 16.8 μg•hr/ml, respectively. Ratio was calculated by dividing animal Day last AUC_{0-24} or C_{max} values by respective human values.

[b] Phenotype: Fast are dogs of the phenotype that eliminate SC-58635 from plasma at a fast rate. Slow are dogs of the phenotype that eliminate SC-58635 from plasma at a slow rate.

5.3.2. *TISSUE DISTRIBUTION*

Celecoxib was well distributed into the majority of tissues as demonstrated by a rat tissue distribution study. Following an oral dose of 2 mg/kg [ ]celecoxib, the gastrointestinal tract tissues contained the highest concentrations of radioactivity, with high levels of radioactivity also found in liver, red blood cells, adrenal glands, lacrimal glands and bone marrow. The concentrations of radioactivity in skin were the same as that of plasma, indicating that there was no preferential

partitioning of celecoxib and/or its metabolites into skin. The concentrations of radioactivity in pigmented and nonpigmented skin were similar and decreased at similar rates, indicating no irreversible or extensive binding of celecoxib to melanin. By 96 hours post dose, concentrations of radioactivity in most tissues were below the limit of detection.

Data from the whole-body autoradiography study (iv bolus loading dose of celecoxib at 2 mg/kg followed by a 5-hour IV infusion dose of celecoxib at 0.4 mg/kg/hr) showed that highly perfused tissues, namely liver, heart, lungs, and kidney, and intestinal contents contained the largest amounts of radioactivity. Smaller levels of radioactivity were observed in the stomach, lining of the cecum and intestines, harderian gland, adrenal gland, pancreas, bone marrow, blood, brain, spinal cord, testes, skin and hair follicles.

5.3.3. METABOLISM

Celecoxib was metabolized by a single metabolic pathway in all species studied (mouse, rat, dog, rabbit, and monkey). Hydroxylation of the aromatic methyl group of celecoxib to form SC-60613 was the initial step in the metabolism of SC-58635. Then, the hydroxyl group of SC-60613 was further oxidized to a carboxyl to form SC-62807. SC-60613 and SC-62807 were metabolites produced by rat, dog, cynomolgus monkey and rhesus monkey. The glucuronide conjugates of SC-60613 and SC-62807 were present in bile of rat. The glucuronide conjugate of SC-62807 and the dual glucuronide glycine conjugate of SC-62807 were present in rabbit urine. SC-60613 and SC-62807 have been synthesized and shown not to have any inhibitory activity to COX-1 or COX-2. The metabolism of celecoxib by the animal species studied was similar to that for human, i.e. hydroxylation of celecoxib to SC-60613 and further oxidation to the carboxylic acid, SC-62807. The 1-O-glucuronide of SC-62907 is a minor metabolite in human.

In vitro metabolism of celecoxib was studied in the rat, dog, and human. Data showed that (1) celecoxib was a mild inducer of CYP2B but not CYP3A in the rat; (2) CYP2D15 was important for the metabolism of celecoxib in the dog; and (3) CYP2C9 and CYP3A4 were the most important cytochrome enzymes involved in the metabolism of celecoxib in the human.

5.3.4. PLASMA PROTEIN BINDING

The plasma protein binding of SC-58635 was evaluated *in vivo*. Approximately 95% of celecoxib bound to plasma protein following oral administration to the mouse, rat and dog. Similar data were noted in the *in vitro* studies. The following table summarizes results expressed as % binding of SC-58635 obtained from *in vitro* protein binding studies.

SC-58635 (µg/ml)	Method	Mouse Plasma	Rat Plasma	Dog Plasma	Human Plasma	Human Albumin (40 mg/ml)[a]	Human AAG (1.8 mg/ml)[a]
0.1		94.4	98.4	98.2	98.2	100	92.4
0.3		ND	94.3	96.7	97.9	100	91.6
1		ND	91.4	97.0	96.5	99.8	91.0
3		ND	95.9	97.0	96.7	99.9	88.4
10		93.5	84.2	97.1	96.3	99.8	78.6
0.3		ND	95.6	ND	97.3	ND	ND
1		ND	85.3	ND	ND	ND	ND
3		ND	88.3	ND	90.6	ND	ND

ND - Not Determined.

AAG = α_1 acid glycoprotein.

[a] These concentrations reflect values in normal human.

5.3.5. EXCRETIONS

Studies in the rat, dog, cynomolgus monkey, and Rhesus monkey showed that biliary/intestinal excretion was the major route for the elimination of celecoxib following a single iv dose with values of 90%, 90%, 65%, and 80%, respectively. The remaining dose was eliminated through urine. SC-62807, the carboxylic acid metabolite, was the major metabolite excreted in both urine and feces. Celecoxib was metabolized extensively in all species studied by the evidence of little or no unchanged drug excreted in urine or bile.

5.3.6. PLACENTAL TRANSFER AND MILK SECRETION

Secretion of celecoxib through milk was evaluated in the lactating SD rats by given a single oral dose of 5 mg SC-58635 via gavage. The concentrations of celecoxib in maternal plasma and milk were similar, indicating that celecoxib was distributed to milk and available to the neonate. In addition, celecoxib was present in plasma of neonates from dams that were administered the test article.

Placental transfer of celecoxib was studied by giving a single oral dose mg/kg celecoxib to pregnant rats (n=18) at approximately day 18 of gestation. Results showed that the concentrations of celecoxib in maternal plasma and fetuses were similar, indicating that celecoxib crossed the placenta and was available to the fetus.

6. CONCLUSION AND RECOMMENDATION:

It appeared that GI and kidney were major target organs for SC-58635 induced toxicity following repeated oral administration to the mouse and rat.

GI injury with low incidence of interdigital pyoderma/subcutis abscess were observed in dogs treated with doses ≥50 mg/kg/day (equivalent to 1.3-4.4x of human exposure at 400 mg/day dose as measured by $AUC_{0-24)}$ for 4-week. **Similar findings of cutaneous lesions were observed in dogs treated with other COX-2 inhibitors. Although these observations occurred at low incidence and did not appear to be dose-dependent, test-article caused toxicity through the mechanism by inhibiting phagocytic cell functions could not be ruled out. Therefore, close monitoring of adverse events of microbial infections in addition to GI injury in humans is highly recommended.** Additionally, there were lesions with slight→mild chronic multifocal perivascular/periventricular lymphocytic infiltrate identified in a dog 4-week toxicity study. These pathological changes within brain are often seen in dogs with viral infection with CNS involvement. Information from a rat study implied that SC-58635 could pass blood-brain-barrier (BBB) and rapidly distribute into CNS tissues as the levels of SC-58635 in CNS were higher than blood following an oral administration of 10 mg/kg. Therefore, the observations of theses changes may be attributable to drug-caused toxicity. It would be beneficial to conduct additional studies to distinguish whether such lesions are drug-induced or due to underlying viral inflammatory diseases of the CNS or other causes.

The effects of SC-58635 on pancreatic functions were not investigated in the current submission. It has been shown that COX-2 constitutively expressed in the pancreatic tissue (HIT-T15 cells, Syrian hamster islets and human pancreatic islets) under basal and stimulated condition[18]. Thus, the pharmacological or undesirable toxicological effects of SC-58635 on β-cells and blood glucose levels following long term use need to be addressed.

Approval of Celebrex™ is recommended.

APPEARS THIS WAY
ON ORIGINAL

W.C. Josie Yang, Ph.D.

Concur by team leader: Yes ☐ No ☐

Andrea Weir, Ph.D.

APPEARS THIS WAY
ON ORIGINAL

[18] Sorli CH, et al., 1998. Proc. Natl. Acad. Sci. USA 95: 1788-1793.

cc:
HFD-550/Division File
/JYang
/AWeir
/JWitter
/MAverbuch
/VLutwak
HFD-345

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL